Characterising recent mortality trends in people with bipolar disorder and schizophrenia in England using linked hospital and mortality data

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Characterising recent mortality trends in people with bipolar disorder and schizophrenia in England using linked hospital and mortality data

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Declaration

The work presented in this thesis was conceived, designed, executed and written entirely by me.

Dr Uy Hoang

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Abstract

Background and objectives

Mortality is higher in people with severe mental illness than others. An important policy goal is to reduce this 'mortality gap'. The objectives of this thesis were to investigate whether the gap has reduced in recent years in people with bipolar disorder or schizophrenia, to quantify the extent of 'avoidable mortality' in these people, and to investigate whether the excess mortality risk extends to people with a physical illness as a main diagnosis and comorbid SMI.

Method

Three separate record linkage studies were undertaken study using Hospital Episode Statistics and death registration data about patients discharged from inpatient care in England between 1999 and 2007.

Results

Findings showed that the mortality gap widened over the last decade for people with bipolar disorder and schizophrenia. For people discharged with bipolar disorder the SMR increased from 1.3 to 1.9 between 1999 and 2006 (Poisson test of trend, P=0.06). Whilst for people discharged with schizophrenia the SMR increased from 1.6 to 2.2 (P<.001). Potentially avoidable deaths comprised 59·2% and 60.2% of all deaths in people with a diagnosis of bipolar disorder and schizophrenia respectively. The results showed that comorbidity with mental illness in people with a main diagnosis of CVD causes between 12-46% excess deaths compared with those without mental comorbidity, and between 43-68% excess deaths in people with a main diagnosis of Diabetes.

Conclusion

The total burden of premature deaths in these populations is substantial and increasing. Current approaches to reduce mortality would be expected to reduce the overall mortality

excess in SMI by about 50%, but not eliminate it entirely. These results strongly point to the need for better understanding of the reasons for the persistent mortality gap; and for continued action to target risk factors for both natural and unnatural causes of death in people with SMI.

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bipolar disorder, schizophrenia, comorbidity,
mortality, avoidable mortality

List of tables

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Glossary of abbreviations

ACF	Academic Clinical Fellow
ACS	Acute Coronary Syndromes
APA	American Psychiatric Association
BMJ	British Medical Journal
CI	Confidence Interval
CIPS	Continuous Inpatient Spell
CPN	Community Psychiatric Nurses
CRIS	Clinical Record Interactive Search
CVD	Cardiovascular disease
DH	UK Department of Health
DM	Diabetes Mellitus
DOB	Date of Birth
DSH	Deliberate Self Harm
DSM-IV	Diagnostic & Statistical Manual of Mental Disorders version 4
EPA-EU GEI	European Psychiatric Association & European network of national networks studying Gene-Environment Interactions
FCE	Finished Consultant Episodes
FDA	US Food and Drug Administration
FU	Follow-Up
GAS	Goal Attainment Scaling
GP	General Practitioners
GPRD	General Practice Research Database
HES	Hospital Episode Statistics
HESID	HES Patient ID
HR	Hazard Ratio
IHD	Ischaemic Heart Disease
ICD	International Classification of Diseases

IMD	Index of Multiple Deprivation
IoP	Institute of Psychiatry
KCL	Kings College London
MHMDS	Mental Health Minimum Dataset
MMF	Master Matching File
MOOSE	Meta-analysis Of Observational Studies in Epidemiology
MS	Microsoft
NHS	UK National Health Service
NHS IC	NHS Information Centre
NICE	National Institute for Health and Clinical Excellence
ONS	UK Office for National Statistics
OR	Odds Ratio
ORLS	Oxford Record Linkage Study
OxSPH	Oxford School of Public Health
OUCAGS	Oxford University Clinical Academic Graduate School
PCD	Postcode
QOF	Quality Outcomes Framework
RCP	Royal College of Physicians
RCPsych	Royal College of Psychiatry
RCT	Randomised Controlled Trial
RO	Government Regional Office
RR	Relative Risk
SAS	Statistical Analysis System
SD	Standard Deviation
SE	Standard Error
SGA	Second Generation Anti-psychotic
SMI	Severe Mental Illness
SMR	Standardised Mortality Ratio

SpR	Specialist Registrar
UHCE	Unit of Health-Care Epidemiology, University of Oxford
UK	United Kingdom
UK DH	UK Department of Health
UK ONS	UK Office for National Statistics
US	United States
VA/ VHA	US Veterans Health Administration
VBA	Visual Basic
WHO	World Health Organisation
YPLL	Years of Potential Life Lost

Mortality terms used

Term	Definition
Mortality	Cessation of life (Last 2006)
All-cause mortality	Cessation of life as a result of any cause
Specific cause mortality	Cessation of life as a result of a specific cause/ s
Avoidable cause mortality	Cessation of life from a potentially avoidable cause/ s (Wheller, Baker et al. 2007; 2011)
Mortality outcomes	The occurrence of a cessation of life, as a result of exposure to a risk or the manner in which a health problem has been managed
Mortality research/ studies	Research relating to the cessation of life
Mortality data/ datasets/ records	Data containing information on the cessation of life
Mortality risk	The probability or odds that death will occur (Last 2006)
Mortality risk profile	The probability or odds that death will occur (Last 2006)
Absolute mortality risk	The probability or odds that death will occur in a specified population
Relative mortality risk	The probability or odds that death will occur in a specified study population compared with a comparison population of equivalent age-sex
Risk of death	Predisposition to cessation of life
Mortality experience	Knowledge or skills based on personal observations or contacts around death
Mortality rate	A general term for rates compiled from data on the number of deaths in relation to a specified population at risk (Last 2006)
Absolute mortality rate	The mortality rate in a specified population
Relative mortality rate	The mortality rate in a specified study population compared with a comparison population of equivalent age-sex

Mortality excess	The number, rate or probability of death in the study population over and above that in the comparison population
Mortality gap	The difference between the number, rate or probability of death in the study population and the comparison population taking into account the age-sex structure of each population
Mortality trend	A series of measures of the number, rate or probability of death calculated to show a pattern of increasing or decreasing magnitude over time

Publications from the thesis

See also Appendix 1.

Mortality after hospital discharge for people with schizophrenia or bipolar disorder: retrospective study of linked English hospital episode statistics, 1999-2006 by Hoang U, Stewart R and Goldacre MJ, BMJ 2011;343:d5422

Avoidable mortality in people with severe mental illness: a cohort study of people recently discharged from hospital in England, by Hoang U, Goldacre MJ and Stewart R. Acta Psychiatrica Scandinavica, March 2013, Volume 127, Issue 3, pages 195–201

Outline of the thesis

The thesis starts with an introduction to mental illness, including a review of the terms used in this thesis, and the conditions - bipolar disorder and schizophrenia - that are the focus of this work.

In chapter 2, I review the relevant literature pertaining to mortality in people with severe mental illness, especially focusing on studies undertaken within the last decade in people with bipolar disorder and schizophrenia.

Chapter 3 lays out the gaps in the literature, and chapter 4 states the specific objectives of this thesis and the hypotheses that will be explored.

Chapter 5 outlines the core methods that will be used to undertake the studies within this thesis, including a consideration of the use of routinely collected data, especially hospital episode statistics (HES) and death certification records for psychiatric mortality research, the diagnostic codes used to specify the study groups, the mortality outcomes explored and the statistical analysis employed to quantify trends in mortality.

Chapter 6 presents the first study looking at recent trends in all-cause mortality for those who have recently been discharged from inpatient care with a main diagnosis of bipolar disorder or schizophrenia in England and explores the mortality gap between these people and the general population.

Chapter 7 presents the contribution of avoidable causes of death to the mortality gap, namely deaths that are currently considered to be amenable to high quality medical care and those that are preventable given access to public health interventions that are currently available in England. By introducing the concept of the hypothetical standardised mortality ratio (SMR),

this chapter seeks to answer the question about what is possible with current medical and public health interventions.

Chapter 8 explores the risk of death in those who are discharged from hospital with bipolar disorder or schizophrenia not as the main reason for admission, but rather as a comorbid condition in combination with another illness.

Chapter 9 summaries the findings from this thesis, and touches on the implications for current mental health policy and future research

Chapter 1 - Introduction

Mental health and mental disorder

According to the World Health Organisation (WHO) health is defined as *'a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity'(*1946*)*. This holistic definition incorporates attributes of the individual such as their ability to cope with stressors and their resilience to adverse life events, as well as the social and environmental context in which they live. It acknowledges the close relationship between physical and mental health, and recognises that the risks to mental health are influenced by a wide range of socio-economic, interpersonal and hereditary factors (Rutter 1985; Secker 1998; Ewles 2005). It gives justification for the use of public health tools and health policy research to better understand and influence mental health (2001). Importantly, as the definition does not draw a distinction between mental health and mental disorder, it suggests that anyone can have good mental health, regardless of whether or not they have a mental disorder.

For clinical practice, mental disorders have been defined as 'conditions in which reduced mental, emotional and/or intellectual capacity renders individuals unable to function fully, or normally in society' (Thornicroft 2001; Patel 2002; Last 2006).This definition includes disorders such as mental retardation which are present from early life, as well as those conditions where there is an identifiable onset of illness preceded by normal functioning (Katona and Robertson 2000). Two well recognised taxonomic systems are currently used to group these conditions into categories based upon the profile of symptoms presented by people themselves, and signs elicited by clinicians (King 1999; Katona and Robertson 2000; Dalal and Sivakumar 2009). The first is the International Classification of Diseases revision 10 (ICD10), produced by the WHO, in which the fifth chapter covers mental and behavioural disorders. The ICD10 taxonomy as a whole relies on the clinician matching symptoms and signs from the presenting client with descriptions of over 14,000 different, separate and

mutually exclusive conditions, including physical illnesses. Under this alpha-numeric classification system, every health condition can be assigned to a unique category and given a code, up to six characters long (WHO website). Mental disorders are classified into ten main groups:

F0: Organic, including symptomatic, mental disorders

F1: Mental and behavioural disorders due to use of psychoactive substances

F2: Schizophrenia, schizotypal and delusional disorders

F3: Mood [affective] disorders

F4: Neurotic, stress-related and somatoform disorders

F5: Behavioural syndromes associated with physiological disturbances and physical factors

F6: Disorders of personality and behaviour in adult persons

F7: Mental retardation

F8: Disorders of psychological development

F9: Behavioural and emotional disorders with onset usually occurring in childhood and adolescence

In addition, there is a residual group of "unspecified mental disorders". ICD10 is an example of a categorical classification system in which conditions are grouped separately and hierarchically, so that a person can receive only one main diagnosis (WHO ; Kessler 2002; Rosenman, Korten et al. 2003).

The second taxonomy for mental health is the Diagnostic and Statistical Manual of Mental Disorders version 4 (DSM-IV) produced by the American Psychiatric Association (APA) and currently used in its fourth version (DSM-IV). This classification relies on an evaluation of the client along five operational criteria or axes: clinical disorder, excluding personality and mental retardation (axis 1), personality disorders and mental retardation (axis 2), somatic conditions connected to the mental disorder (axis 3), psychosocial and environmental problems (axis 4), global assessment of functioning (axis 5). In order to categorise a condition, clinicians are required to note which symptoms are present within each axis,

including the time they are present, and the presence of exclusion criteria (APA ; Stein, Phillips et al. 2010). This multiaxial classification system rates clients' presenting complaints along several weighted categorical scales each measuring a different aspect of the presentation (Katona and Robertson 2000). The main categories of disorder in the DSM are:

- Disorders usually first diagnosed in infancy, childhood or adolescence
- Delirium, dementia, and amnesia and other cognitive disorders
- Mental disorders due to a general medical condition not elsewhere classified
- Psychoactive substance-related disorders
- Schizophrenia and other psychotic disorders
- Mood disorders
- Anxiety disorders
- Somatoform, factitious and dissociative disorders
- Eating disorders
- Sleeping disorders
- Impulse control disorders not elsewhere classified
- Adjustment disorders

There has been substantial convergence between the two classification systems in recent years, but diagnoses recorded using older versions of these classification systems are harder to compare (Berrios 1999; Dalal and Sivakumar 2009).

Specific criticisms of these taxonomies have been raised by proponents of a dimensional system of classification as they argue that attempts to demonstrate natural boundaries between related syndromes, or between a common syndrome and normality have failed (Kessler 2002; Rosenman, Korten et al. 2003; Craddock and Owen 2007). Still others have argued that these definitions of mental disorder lack applicability across cultures, as the diagnosis is so dependent on the ability to function fully, or normally in one's own society (Kleinman, Eisenberg et al. 1978; Alarcon, Becker et al. 2009). Others have observed that

psychiatric diagnoses are not stable over time, and suggest that they may be susceptible to diagnostic fashions (Paris 2004; Baca-Garcia, Perez-Rodriguez et al. 2007). Lastly concerns have been raised that these classifications give no objective indication of the severity of the mental disorder and the need for mental health services (1999). Despite the ongoing criticism of the validity and reliability of psychiatric taxonomies, these diagnoses are still widely used in clinical practice, and attempts have been made to improve inter-rater reliability for epidemiological research (Kendell and Jablensky 2003; Aboraya 2007).

A pragmatic classification based on symptom severity, disability and health service use has been proposed to classify mental disorders into mild, moderate and severe (1999; Charlwood, Mason et al. 1999). Examples of severe mental illness include schizophrenia, bipolar affective disorder (manic depression), organic mental disorder (dementia), severe anxiety disorders, severe eating disorders, severe depression, and severe panic disorder. However there is little consistency in how these pragmatic categories especially severe mental illness (SMI), the most frequently used category, are defined in practice (Schinnar, Rothbard et al. 1990; Slade, Powell et al. 1997; Ruggeri, Leese et al. 2000). This limits the usefulness of this taxonomy for epidemiological research.

Bipolar disorder and schizophrenia

These conditions are classified as psychotic disorders as they are characterised by a noticeable separation of the normal links between perception, mood, thinking, behaviour and contact with reality. People experiencing severe episodes of these disorders can present with delusions (i.e. fixed, false, unshakable beliefs), hallucinations (i.e. perceptions without stimuli, for example hearing voices), and disorganised thinking/ speech or behaviour. People with bipolar disorder may also present with these symptoms, although recurrent swings of mood is a more cardinal feature of this condition (Katona and Robertson 2000; Gelder, Andreasen et al. 2009).

Emil Kraepelin first classified psychosis into organic psychosis, where a physiological disturbance can be shown, and functional psychosis, where no such disturbance can be demonstrated (Kraepelin 1893). This classification corresponds broadly to the current taxonomy for schizophrenia used in ICD10 and DSM-IV (see Table 1-1). Bipolar disorder has traditionally been classified according to the pattern of mood disturbance. People with bipolar disorder I have one or more manic or mixed episodes, and one or more major depressive episodes, whereas people with bipolar II have recurrent depressive and hypomanic episodes, but no manic episodes. People with cyclothymia have chronic mood fluctuations with no evidence of mania or depressive episode sufficient to meet criteria for major depression (Katona and Robertson 2000; Gelder, Andreasen et al. 2009). This classification is adopted by the DSM-IV taxonomy.

Aetiology and pathophysiology

The exact aetiology of both of these conditions has not currently been elucidated, but it is thought to be multifactorial, with evidence for important genetic/ familial and environmental contributions (Belmaker 2004; Picchioni and Murray 2007; Van Os and Kapur 2009), see Table 1-2.

A number of structural and physiological changes have been reported in both conditions. In schizophrenia, structural brain imaging studies have found associations with subtle decreases in grey matter, enlargement of ventricles, and focal alteration of white matter tracts (Vita, De Peri et al. 2006; Glahn, Laird et al. 2008; Ellison-Wright and Bullmore 2009). Neurochemical studies have found that the acute psychotic state in schizophrenia is associated with an increase in dopamine synthesis, dopamine release, and resting-state synaptic dopamine concentrations (Laruelle 1998; Guillin, Abi-Dargham et al. 2007) and the 'dopamine hypothesis' attributes psychosis to faulty interpretations arising from misfiring dopaminergic neurons (Van Os and Kapur 2009). In contrast bipolar disorder has been found to be associated with abnormalities in the lateral ventricular and globus pallidus, and with deep white matter hyperintensities (Kempton, Geddes et al. 2008; Arnone, Cavanagh et al.

2009). Evidence of neuroendocrine abnormalities has been inconsistent but suggest abnormalities in the hypothalamic-pituitary-adrenal axis (HPA axis) may be an important (Katona and Robertson 2000; Plocka-Lewandowska, Araszkiewicz et al. 2001; Watson, Gallagher et al. 2004).

Table 1-1 - ICD10 and DSM-IV codes for bipolar disorder and schizophrenia

Bipolar disorder	Schizophrenia
International Classification of Diseases version 10 (ICD10)	
F31 – Bipolar affective disorder • F31.0 - Bipolar affective disorder, current episode hypomanic • F31.1 - Bipolar affective disorder, current episode manic without psychotic symptoms • F31.2 - Bipolar affective disorder, current episode manic with psychotic symptoms • F31.3 - Bipolar affective disorder, current episode mild or moderate depression • F31.4 - Bipolar affective disorder, current episode severe depression without psychotic symptoms • F31.5 - Bipolar affective disorder, current episode severe depression with psychotic symptoms • F31.6 - Bipolar affective disorder, current episode mixed • F31.7 - Bipolar affective disorder, currently in remission • F31.8 - Other bipolar affective disorders • F31.9 - Bipolar affective disorder, unspecified	F20 to F29 – Schizophrenia, schizotypal and delusional disorders • F20 – Schizophrenia • F21 – Schizotypal disorder • F22 - Persistent delusional disorders • F23 - Acute and transient psychotic disorders • F24 - Induced delusional disorder • F25 - Schizoaffective disorders • F28 - Other nonorganic psychotic disorders • F29 – Unspecified nonorganic psychosis
Diagnostic and Statistical Manual of Mental Disorders version 4 (DSM-IV)	

Bipolar I disorder, single manic episode
• 296.00 Unspecified
• 296.01 Mild
• 296.02 Moderate
• 296.03 Severe without psychotic features
• 296.04 Severe with psychotic features
• 296.05 In partial remission
• 296.06 In full remission
 	
Bipolar I disorder, most recent episode manic
• 296.40 Unspecified
• 296.41 Mild
• 296.42 Moderate
• 296.43 Severe without psychotic features
• 296.44 Severe with psychotic features
• 296.45 In partial remission
• 296.46 In full remission
 	
Bipolar I disorder, most recent episode depressed
• 296.50 Unspecified
• 296.51 Mild
• 296.52 Moderate
• 296.53 Severe without psychotic features
• 296.54 Severe with psychotic features
• 296.56 In full remission
• 296.55 In partial remission
	• Psychotic disorder secondary to general medical condition
	  ○ 293.81 With delusions
	  ○ 293.82 With hallucinations
	• 295.10 Disorganized type
	• 295.20 Catatonic type
	• 295.30 Paranoid type
	• 295.40 Schizophreniform disorder
	• 295.60 Residual type
	• 295.70 Schizoaffective disorder
	• 295.90 Undifferentiated type
	• 297.1 Delusional disorder
	• 297.3 Shared psychotic disorder
	• 298.8 Brief psychotic disorder
	• 298.9 Psychotic disorder NOS

Bipolar I disorder, most recent episode mixed

- 296.60 Unspecified
- 296.61 Mild
- 296.62 Moderate
- 296.63 Severe without psychotic features
- 296.64 Severe with psychotic features
- 296.65 In partial remission
- 296.66 In full remission
- 296.7 Bipolar I disorder, most recent episode unspecified
- 296.80 Bipolar disorder NOS
- 296.89 Bipolar II disorder
- 301.13 Cyclothymic disorder

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Table 1-2 - Aetiology of bipolar disorder and schizophrenia

Bipolar Disorder	Schizophrenia
Evidence for genetic contributions	
• Bipolar disorder is reported with increased frequency in first degrees relatives of those with the condition, but the findings are inconsistent (Kato 2007; Burmeister, McInnis et al. 2008)	• Schizophrenia is reported with increased frequency in relatives of people with schizophrenia (O'Donovan, Williams et al. 2003; Picchioni and Murray 2007)
• Twin studies have found high concordance in monozygotic twins and low concordance in dizygotic twins brought up together, however studies have been limited by small sample sizes (Reich, Clayton et al. 1969)	• Concordance rates are higher in monozygotic twins (Katona and Robertson 2000; O'Donovan, Williams et al. 2003; Picchioni and Murray 2007)
	• Adopted-away offspring of people with schizophrenia have an increased risk of developing schizophrenia (Katona and Robertson 2000; O'Donovan, Williams et al. 2003; Picchioni and Murray 2007)
Evidence for environmental contributions	
• Consistent evidence of high frequency of early life stressors (Leverich and Post 2006)	• Links to season of birth (Torrey, Miller et al. 1997), low birth weight (Rifkin, Lewis et al. 1994; Smith, Flynn et al. 2001), maternal viral infection (Kirch 1993; Yolken and Torrey 1995; Brown 2006) and other early life exposures has been found (Khashan, Abel et al. 2008)
• Evidence that recent life events and interpersonal relationships contribute to the likelihood of onsets and recurrences of bipolar mood episodes (Alloy, Abramson et al. 2005)	• Tentative associations have been found with abnormal family processes including problem parenting, and acute life stressors (Picchioni and Murray 2007; Larkin and Read 2008)

Epidemiology

Both bipolar disorder and schizophrenia are relatively rare conditions, with the incidence of schizophrenia reported to be 15-20/ 100,000 per year, and the lifetime morbidity risk to be 0.85% (McGrath, Saha et al. 2008; Van Os and Kapur 2009), whilst for bipolar disorder the lifetime prevalence is 1 - 2% (bipolar disorder I) (Ketter 2010). Late adolescence and early adulthood are peak years for the onset of both conditions (Belmaker 2004; Picchioni and Murray 2007; Van Os and Kapur 2009), with a long tail of later onset cases extending into old age (Howard, Rabins et al. 2000; Howard 2010). Schizophrenia is seen more frequently in men where it often appears at an earlier age (Castle, Wessely et al. 1993; Roy, Maziade et al. 2001; Picchioni and Murray 2007; Van Os and Kapur 2009), in contrast to bipolar disorder, which has a slight excess in women (Belmaker 2004).

Clinical presentation

Kurt Schneider described a list of first-rank symptoms that he considered pathognomonic of schizophrenia, that could be used to distinguish the condition from other psychotic disorders. These include audible thoughts (or thought echo), thought withdrawal, thought insertion, thought broadcasting, somatic/thought passivity, and delusional perception (Schneider 1959). However, recent evidence suggests that these symptoms lack specificity (Nordgaard, Arnfred et al. 2008).

The symptoms originally described by Schneider, with subsequent modifications, are also often characterised as positive symptoms, which are judged typically to respond well to anti-psychotic medications (Picchioni and Murray 2007; Van Os and Kapur 2009). In addition, people with schizophrenia can often experience deficits in their normal emotional response, such as flat or blunted affect and emotion, poverty of speech (alogia), inability to experience pleasure (anhedonia), lack of desire to form relationships (asociality), and lack of motivation (avolition), symptoms which respond less well to anti-psychotic medications (Andreasen, Flaum et al. 1990; Murphy, Chung et al. 2006).

Table 1-3 - ICD-10 diagnostic criteria for a diagnosis of schizophrenia

At least one present for most of the time for a month	• Thought echo, insertion or withdrawal, or thought broadcast • Delusions of control referred to body parts, actions, or sensations • Delusional perception • Hallucinatory voices giving a running commentary, discussing the patient, or coming from some part of the patient's body • Persistent bizarre or culturally inappropriate delusions
Or at least two present most of the time for a month	• Persistent daily hallucinations accompanied by delusions • Incoherent or irrelevant speech • Catatonic behaviour such as stupor or posturing • Negative symptoms such as marked apathy, blunted or incongruous mood

Bipolar disorder is characterised by alterations of mood rather than being primarily a disorder of thought processing, as described above. Distinct periods of elevated, expansive mood known as mania, and commonly associated with increased psychomotor activity, seen as rapid thinking, pressured speech, distractibility, and decreased need for sleep; reduced social inhibition, which can be result in sexual over-activity, overspending, substance abuse and inappropriate business, religious or political activity can occur in some clients with this disorder. Mood congruent thought disorders such as grandiose delusions/ hallucinations are also common and are reflective of the client's elevated mood and exaggerated optimism. Equally severe anxiety or irritability are also commonly experienced by people during an acute manic episode. Mood incongruent psychotic features may also be found, and may indicate a schizoaffective disorder. The elevated symptoms must last for at least one week if the diagnosis of bipolar I disorder is to be considered. In comparison, hypomania is generally a mild to moderate level of mood elevation, characterized by optimism, pressure of speech and activity, and decreased need for sleep, which does not limit functioning. ICD10 diagnostic criteria stipulate that a diagnosis of bipolar disorder can only be made when there is evidence of two or more episodes in which the patient's mood and activity levels are significantly disturbed, this disturbance consisting on some occasions of an elevation of mood and increased energy and activity (hypomania or mania) and on others of a lowering of mood and decreased energy and activity (depression)(WHO). During the depressive phase of bipolar disorder clients may experience persistent feelings
of sadness, anxiety, guilt, anger, isolation, or hopelessness; disturbances in sleep and appetite; fatigue and loss of interest in usually enjoyable activities; problems concentrating; loneliness, self-loathing, apathy or indifference; depersonalization; loss of interest in sexual activity; shyness or social anxiety; irritability, chronic pain (with or without a known cause); lack of motivation; and morbid suicidal ideation (Katona and Robertson 2000; Belmaker 2004).

Clinical management and current public health approaches in the UK

Unfortunately there is no objective test for either condition, thus diagnosis is based upon confirmation of the key symptoms, and the exclusion of the most likely differential diagnoses. There is currently no cure for these disorders, and both are considered long-term conditions. However recent longitudinal studies with long follow-up periods have found that up to 50% of people diagnosed with schizophrenia have a moderately good long-term global outlook with extended periods of stable mental health, and that people who never experience complete recovery can still manage to sustain an acceptable quality of life with adequate support and help (Gaebel and Frommann 2000; Harrison, Hopper et al. 2001; Jobe and Harrow 2005). The long-term outlook for clients with bipolar disorder is similar to schizophrenia and is very dependent upon successful ongoing care and engagement (Coryell, Turvey et al. 1998; Turvey, Coryell et al. 1999; Angst and Sellaro 2000). Thus clinical management of both conditions revolves around early diagnosis, the prompt treatment of acute psychiatric episodes, reintegration into the community, and the prevention of further acute psychiatric events and complications including physical ill-health (Katona and Robertson 2000; Belmaker 2004; Picchioni and Murray 2007; Gelder, Andreasen et al. 2009; Van Os and Kapur 2009).

There are a number of options for the treatment of acute psychiatric events depending on the severity of symptoms, however pharmacological treatment is still the mainstay of acute management (Health 2010). Hospitalisation is often necessary for the first or subsequent severe episodes. There is substantial overlap between the pharmacological treatments used to treat acute episodes of each condition, namely acute psychosis and mania with the use of anti-psychotic drugs, which block dopamine D2 receptors being the drugs of choice for acute management as a result of their non-specific sedative effects, as well as their specific effects on decreasing positive symptoms (Kapur and Mamo 2003; El-Mallakh, Elmaadawi et al. 2010).

Over the last decade there has been a growing number of so-called ‘second-generation’ or ‘atypical’ anti-psychotics, which have been introduced into clinical practice (Agid, Kapur et al. 2008; Kane and Correll 2010). These drugs have been said to have a better side effect profile than older ‘first generation’ anti-psychotics, especially reduced occurrence of motor side-effects, and to be better tolerated by clients (Keck, Strakowski et al. 2000; Leucht, Corves et al. 2009), although this has been disputed (Jones, Barnes et al. 2006; Lewis, Davies et al. 2006). They are also thought to have an effect on reducing negative symptoms (McElroy, Guerdjikova et al. 2010). However there is increasing evidence that anti-psychotic drugs, including second generation anti-psychotics have wide-ranging adverse effects on physical health, by inducing metabolic side-effects such as increased triglyceride/ cholesterol levels (De Hert, Schreurs et al. 2009), weight gain (Faulkner, Soundy et al. 2003), as well as increased risk of type 2 diabetes (Group 2004; Group 2004; McIntyre, Konarski et al. 2005; Suvisaari, Perala et al. 2008; Kessing, Thomsen et al. 2010; Schoepf, Potluri et al. 2012) and cardiovascular disease (Glassman 2005; Hennekens, Hennekens et al. 2005).

Anti-psychotic medications are only part of the treatment regime. The combination of new medications, community case management and wider psychosocial interventions, including supportive psychotherapy, occupational therapy, counselling and family therapy can help ameliorate symptoms, reduce the length and cost of hospital stay, increase compliance with medical treatments, improve functioning and client satisfaction, and prevent relapse, although the availability of these complementary services is often limited (Falloon, Boyd et al. 1985; Leff, Berkowitz et al. 1990; Pilling, Bebbington et al. 2002; Burns, Catty et al. 2007; Picchioni and Murray 2007; Van Os and Kapur 2009; Marshall and Lockwood 2011) and controversial, especially when combined with ‘minimal medication’ or ‘whole body’ approaches to the treatment of SMI (Carpenter 1997; Calton and Spandler 2009).

Depressive episodes in clients with bipolar disorder generally respond well to anti-depressant therapy, although caution is needed to avoid a switch from depression to mania, especially in people with a history of severe manic episodes (Kusumakar 2002).

After recovery from an acute episode of schizophrenia, current guidance from the National Institute of Clinical Excellence (NICE) recommends prophylactic doses of anti-psychotics for one or two years with continued specialist supervision (2009) and intra-muscular administration if there are problems with non-compliance (McEvoy 2006).

For people with bipolar disorder long-term management also relies on pharmacological and non-pharmacological strategies. 'Mood stabilising' drugs, such as lithium, sodium valproate carbamazepine or lamotrigine are the mainstay of long-term pharmacological management (Bauer and Mitchner 2004; Geddes, Burgess et al. 2004). These drugs act too slowly (Verdoux, Gonzales et al. 1996), but have a better side-effect profile for long-term therapy than anti-psychotic drugs and are better tolerated by clients (Kusumakar 2002; Belmaker 2004). Psychotherapy is aimed at recognizing episode triggers including prodromal symptoms before full-blown recurrence, reducing negative expressed emotion in relationships, and, practicing the factors that lead to maintenance of remission (Zaretsky, Rizvi et al. 2007).

Physical illness and mortality in people with severe mental illness, including bipolar disorder and schizophrenia

Growing evidence has suggested a close relationship between physical and mental health, especially in people with severe mental illness (SMI) such as bipolar disorder and schizophrenia, who are at increased risk from a wide range of physical illnesses, including coronary heart disease, diabetes, respiratory disease and infections (Barr 2001; Phelan, Stradins et al. 2001; Leucht, Burkard et al. 2007; 2009). although the association between these conditions and cancer is less clear (Goldacre, Kurina et al. 2005; Hodgson, Wildgust et al. 2010). The underlying reasons for these relationships is complex, and not yet fully understood, but are thought to include; 1) factors related to the mental disorder, such as unhealthy behaviours (e.g. high levels of smoking, substance abuse, unhealthy diets and

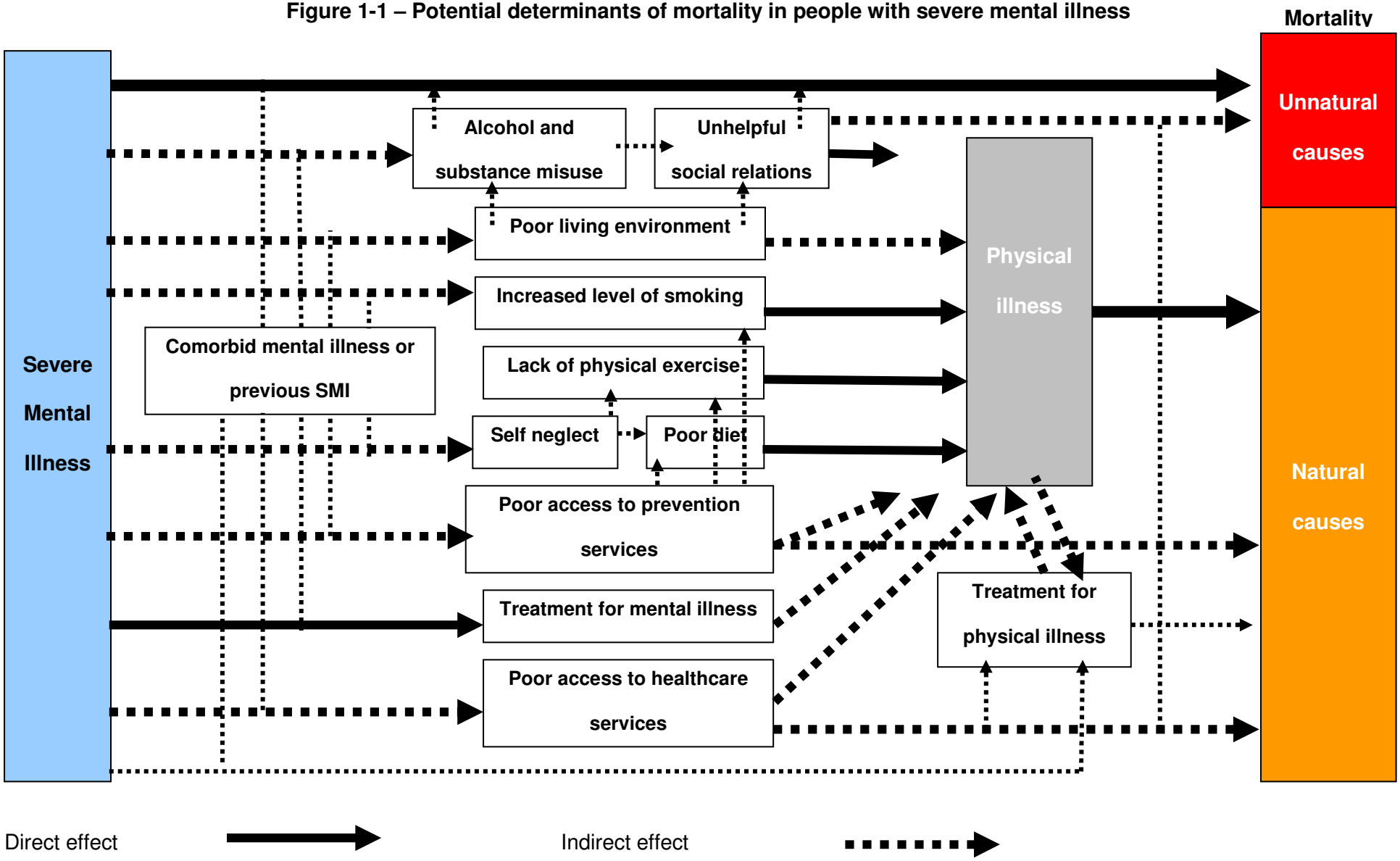
inactivity) which have been found to be increased in these populations (Brown, Birtwistle et al. 1999); 2) factors related to the treatment of the mental disorder, including the metabolic side effects of anti-psychotic medications (De Hert, Schreurs et al. 2009); and 3) factors unrelated to the mental disorder or treatment, but connected to the social context in which the client with severe mental illness live. For example, an increasing amount of recent research shows that people with severe mental illness experience stigma (Fink and Tasman 1992; Byrne 1999; Sartorius 2002), and discrimination (Wahl and Lefkowits 1989; Coverdale, Nairn et al. 2002; Sieff 2003; Stuart 2006; Thornicroft 2006) which may result in them having difficulty accessing appropriate treatments, including preventative health measures (Lawrence and Kisely 2010), and difficulty with engaging in physical healthcare treatment. Previous research that has investigated the effect of inequality on health has found that how individuals and communities feel, their levels of trust, tolerance and participation, may be critical in determining health (Wilkinson 1996; Kawachi, Kennedy et al. 1997; Wilkinson 2000). 4) factors related to the prenatal period, or early development, with some authors suggesting that schizophrenia may be the expression of genetic predisposition or other downstream influences such as low-birth weight, maternal smoking/ alcohol use and maternal virus infections which is shared with other physical illnesses (Leucht, Burkard et al. 2007).

People with SMI have also been found to be at higher risk of mortality than the general population, both as a result of natural causes (Goldacre, Seagroatt et al. 1993; Harris and Barraclough 1997; Hall, O'Brien et al. 1998; 1999; Hiroeh, Appleby et al. 2001; Osby, Brandt et al. 2001; 2002; 2002; Gau and Cheng 2004; Goff, Cather et al. 2005; Tsai, Lee et al. 2005; 2008; Hiroeh, Kapur et al. 2008; Roshanaei-Moghaddam and Katon 2009; Chang, Hayes et al. 2011) and unnatural causes (Goldacre, Seagroatt et al. 1993; Harris and Barraclough 1997; Hall, O'Brien et al. 1998; Hiroeh, Appleby et al. 2001; 2002; 2002; Gau and Cheng 2004; Dutta, Boydell et al. 2007; Simon, Hunkeler et al. 2007). In fact researchers have suggested that these conditions should be described as ‘life-shortening diseases’ (Allebeck 1989). Studies that have attempted to compare the mortality risk profiles of people with

bipolar disorder and schizophrenia have typically found a mortality excess of between 218 and 283% from all-causes of death in these populations (Saha, Chant et al. 2007), with a reduced life expectancy of between 10-20 years (Chang, Hayes et al. 2010).

The high level of physical illness and the mortality risk has been increasingly recognised by healthcare policy makers, and over the past decade several strategies have been implemented in England and Wales aimed at reducing the 'mortality gap' between people with SMI and the general population. This has included strategies aimed at reducing deliberate self-harm and suicide (1999; 2002; 2002), smoking (2008; 2008; 2009; Banham and Gilbody 2010; Tsoi, Porwal et al. 2010; 2011), alcoholism, and drug misuse (2007; 2007), and other lifestyles associated with increased mortality (2004; 2011).

Figure 1-1 – Potential determinants of mortality in people with severe mental illness



Recent studies have suggested that the rate of suicide and unnatural deaths has been stabilising among people with mental disorders as a whole (2005; Griffiths, Wright et al. 2006; Kapur, Hunt et al. 2006; Biddle, Brock et al. 2008; Bowers, Banda et al. 2010). However, recent trends in all-cause mortality for people with schizophrenia and bipolar disorder in England have remained poorly characterised, and there is evidence from other countries that the overall mortality risk for these populations may be increasing (Saha, Chant et al. 2007; Lawrence, Kisely et al. 2010).There are a number of reasons to believe that the mortality risk in these populations (or at least the characteristics of the mortality gap between these populations, and the general population) may have changed over the past decade, including;

- increasing use of second generation anti-psychotics (Santamaria, Perez et al. 2002; Aparasu, Bhatara et al. 2005; Caceres, Penas-Lledo et al. 2008; Ilyas and Moncrieff 2012) despite better awareness of their adverse effects (Fontaine, Heo et al. 2001; Ray, Meredith et al. 2001; Ray, Meredith et al. 2001; Davidson 2002; Witchel, Hancox et al. 2003; Casey, Haupt et al. 2004; Straus, Bleumink et al. 2004; Joukamaa, Heliovaara et al. 2006; Ucok and Gaebel 2008; De Hert, Dekker et al. 2009; Ray, Chung et al. 2009; Correll and Nielsen 2010; Raedler 2010)
- use of anti-psychotic drugs in vulnerable populations including children (Cheng-Shannon, McGough et al. 2004; Najjar, Welch et al. 2004; Aparasu and Bhatara 2005) and older people (Lee, Gill et al. 2004; Rapoport, Mamdani et al. 2005; Citrome 2007; Chahine, Acar et al. 2010; Leon, Gerretsen et al. 2010; Narang, El-Refai et al. 2010) who are at greater risk from the side effects
- increasing evidence that despite the known risk of poor physical health and mortality these populations with SMI have difficulty accessing physical health services (Druss, Bradford et al. 2000; Plomondon, Ho et al. 2007; Laursen, Munk-Olsen et al. 2009; Lawrence and Kisely 2010; Mitchell and Lord 2010; Wildgust and Beary 2010; De Hert, Correll et al. 2011; Scott, Platania-Phung et al. 2011)

- difficulty in engaging these populations with SMI in health improving public health measures that have been implemented over the last decade (Brown, Birtwistle et al. 1999; Alam 2006; Campion, McNeill et al. 2006)

These risk factors may have resulted in an increased prevalence of physical illness in people with bipolar disorder and schizophrenia, or increased the severity of physical illness that presents in these populations, both of which could affect the risk of mortality. Equally, there may have been health improvements in the general population which have failed to reach people with SMI resulting in a widening health inequality gap.

Chapter 2 - Literature review of mortality studies in people with bipolar and disorder schizophrenia

In this chapter a review of the literature on mortality in people with bipolar disorder and schizophrenia is presented, especially focusing on research that has examined the mortality experiences of people with these disorders over the last decade.

Saha and colleagues published a systematic review and meta-analysis of mortality in people with schizophrenia in 2007, which included studies from 1980 to 2006 (Saha, Chant et al. 2007) using guidelines outlined by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group (Stroup, Berlin et al. 2000). They searched a range of databases (MEDLINE, PsychINFO, Web of Science, and Google Scholar) to identify all research studies that investigated mortality in schizophrenia.

Method

In preparing this chapter, the methodology adopted by Saha and colleagues was followed, to update their literature review on mortality in people with schizophrenia. However the search was restricted to publications after 1st January 2000 to focus on evidence elicited on mortality outcomes within the last decade, and also restricted to search to English language journals given the time and cost constraints of this work. Additional search terms for mortality in people with bipolar disorder which was not examined by Saha and colleagues were also used in this literature review. The following broad terms were used to identify suitable titles and abstracts; (schizo* or psych* or bipolar*) for the disorders of interest, followed by (mortality or death) for the outcome of interest.

Potentially relevant articles were accessed and abstracts reviewed. Citations from significant articles and review articles were also scrutinised to locate additional relevant references. The search was restricted to literature published in peer-reviewed journals and materials from the

grey literature or unpublished sources were not sought, and authors were not contacted directly to supply further references given the time and cost constraints of this work.

Studies were included if they met the following criteria: (1) published in peer reviewed literature between 1st January, 2000, and 31st December, 2010, (2) reported deaths in people with bipolar disorder or schizophrenia as diagnosed by any criteria, (3) studied a population 15 years and older, including studies that only had adult populations (>45 years), or older adult populations (>65 years), (4) reported primary data on all-cause mortality and/or specific cause mortality. Studies were excluded if they (1) involved people with a diagnosis other than bipolar disorder or schizophrenia, (2) reported duplicate data, (3) reported only on populations under 15 years of age.

Research

The initial electronic search identified 3044 articles, of which 2866 were excluded because they did not meet the inclusion criteria. The remaining 178 articles possibly meeting inclusion criteria were obtained and their abstracts scrutinised. A further 55 were excluded, leaving 133 that were scrutinised in detail. A summary of the studies identified is included in Appendix 2.

Study designs

There were 19 systematic literature reviews or meta-analyses which focused on the subject of mortality in people with bipolar disorder and schizophrenia. Studies investigating mortality outcomes in SMI utilised a number of observation research strategies.

The majority of the references were to cohort studies, 88 out of 133 studies reviewed using this study design. This involves the identification of a cohort of people with mental disorder from hospital records, community psychiatric registers or community surveys. Data on factors

which may be predictive of mortality are then collected from these subjects and they are followed-up prospectively until death (Mann 2003; Prince, Stewart et al. 2003; Susser, Schwartz et al. 2006; Rothman, Greenland et al. 2008). This follow-up is often undertaken by linking the participants' health records with their death records, using a unique identifying number held on both records, or a set of personal identifiers matched across each health record (Gill, Goldacre et al. 1993; Leadbeter 2000). Frequently a measure of relative mortality risk is calculated by comparing the rate of death in these populations with a suitable comparator group of inpatients or matched community controls without schizophrenia or bipolar disorder. In other studies, the mortality rates in these populations are compared with the mortality rates in the general population to calculate a standardised mortality ratio (SMR).

This methodology has the advantage that the subjects are recruited before the outcome has occurred, and a variety of possible covariates can be taken into account independently of knowledge of the outcome. This minimises the risk of recall bias, an important consideration for case control studies of mortality outcomes (Drew, Kraus et al. 1990). Cohort studies have a number of disadvantages including a large sample size required to enable a robust estimation of mortality risk where the case prevalence is relatively rare. Additionally the follow-up of members of the cohort may require many years and incur considerable cost before the outcome of interest occurs (Mann 2003; Rothman, Greenland et al. 2008). However the cost of follow-up has been considerably reduced with the use of electronic health records and data linkage techniques, enabling outcomes collected from vital statistics such as death certificates to be routinely recorded in follow-up studies. These follow-up methods also reduce the number of subjects lost to follow-up which can bias the estimate of relative risk in cohort studies (Mann 2003; Rothman, Greenland et al. 2008).

Case control studies including nested designs are less often used to study questions regarding mortality. The literature review found a total of 11 studies which used this research method. This involves the selection of a group of people who have died and a age-sex matched group of people who have not died, and calculating the odds of clients with

schizophrenia or bipolar disorder being included in the group that died compared with the group that did not die (Mann 2003; Rothman, Greenland et al. 2008). As the cases and controls are not selected from a general population sample, the absolute risk cannot be calculated, and the relative risk can only be approximated; however the odds ratio calculated from these studies approximates the relative risk when the outcome, in this case mortality, is rare (Greenland and Thomas 1982; Greenland, Thomas et al. 1986; Cummings and Koepsell 2001). These studies may be quicker and cheaper to undertake as there is no requirement to follow-up subjects. However there are considerable weaknesses with this method for examining mortality outcomes, notably the difficulties of obtaining information about exposures, namely a previous history of mental illness, in people who have died mean that these studies are prone to selection and information biases (Drew, Kraus et al. 1990; Mann 2003; Rothman, Greenland et al. 2008).

The majority of the studies investigated mortality in people with schizophrenia (58 studies), followed by broader categories of SMI (33 studies) or psychosis (7 studies), with very few on bipolar disorder specifically (7 studies). The literature review confirmed that people with schizophrenia or bipolar disorder have a higher risk of death than the general population regardless of age or sex. Mortality rates were slightly higher in men than women for both bipolar disorder and schizophrenia, largely as a result of the high rates of unnatural deaths in men.

Sixteen studies reported on data collected from populations in the UK. The all-cause standardised mortality ratios (SMRs) for UK populations with bipolar disorder between 1.2 (Dutta, Boydell et al. 2007) and 2.0 (Chang, Hayes et al. 2010), and for schizophrenia ranged from 1.8 (Dutta, Murray et al. 2010) and 2.9 (Brown, Kim et al. 2010). Deaths from unnatural causes such as suicide were greatly elevated in these groups, with SMRs upto 9.8 for people with bipolar disorder (Dutta, Boydell et al. 2007) , and 11.7 for people with schizophrenia (Dutta, Murray et al. 2010), depending on the cohort sampled and the period of follow-up that was investigated. In fact suicide was the focus of more than 40% of the studies reviewed

from the UK. Deaths from cardiovascular and respiratory disease accounted for the majority of deaths from natural causes in these populations (Brown, Kim et al. 2010). Modifiable or avoidable conditions were also considered an important contributor to mortality in these populations (Rasanen, Hakko et al. 2005; Amaddeo, Barbui et al. 2007; Wildgust and Beary 2010). A summary of the studies in the UK is included in Table 2-1.

Table 2-1 - Mortality studies in the UK on people with bipolar disorder and schizophrenia since 2000

Reference	Summary
Reassessing the long-term risk of suicide after a first episode of psychosis (Dutta, Murray et al. 2010)	Retrospective cohort study of 2723 people presenting for the first time with symptoms of psychosis to hospitals in various locations within the UK over three periods of time between 1965 to 2004, and followed-up for a mean time of 11.5 years. They found that the case fatality from suicide was considerably lower than in previous published research, but the risk of suicide persisted even a decade after 1st presentation, with mean time to suicide of 5.6 years.
All-cause mortality among people with serious mental illness (SMI), substance use disorders, and depressive disorders in southeast London: a cohort study (Chang, Hayes et al. 2010)	Psychiatric case register study in South-East London, between 2007 to 2009, looked at mortality in people with SMI, including schizophrenia and bipolar disorder. Found high all-cause SMRs of 2.2 for people with SMI who accessed services between 2007 to 2009, and also suggested that mortality differs substantially with age, diagnosis, gender and ethnicity.
Suicide amongst psychiatric in-patients who abscond from the ward: a national clinical survey (Hunt, Windfuhr et al. 2010)	Cross-sectional study to describe the social and clinical characteristics of people who had absconded from an in-patient psychiatric ward prior to suicide, using survey based on a 10-year (1997 to 2006) sample of people in England and Wales who had died by suicide. Found 1,851 cases of suicide by current psychiatric in-patients. 469 of these patients died after absconding from the ward. Schizophrenia was the most common diagnosis. Found that absconders were proportionally more likely than in-patients on agreed leave to have been legally detained for treatment, non-compliant with medication, and to have died in the first week of admission
Twenty-five year mortality of a community cohort with schizophrenia (Brown, Kim et al. 2010)	Reports the results from a 25 year follow-up study of a small English community cohort of people with schizophrenia followed from 1981 to 1982. Found a higher rate of all-cause mortality (SMR=2.9), with unnatural deaths concentrated in the first five years of follow-up. They also found that cardiovascular mortality had increased relative to the general population over the course of the study
Psychiatric Hospital Admissions, Behavioral Risk Factors, and All-Cause Mortality: The Scottish Health Survey (Hamer, Stamatakis et al. 2008)	Cohort study using Scottish health survey data linked to HES, and death records to examine the effects of behavioural risk factors on psychiatric hospital use and mortality in people with SMI. They included data on 597 admissions to psychiatric hospitals up to 2003, and followed for mortality to 2006, for a mean period of 8.5 years. They found that mortality was mediated by behavioural risk factors such as socioeconomic status (OR=2.2), history of smoking (OR=4.7) and poor level of physical activity (OR=2.2).
Suicide in current psychiatric in-patients: a case-control study The National Confidential Inquiry into Suicide and Homicide (Hunt, Kapur et al. 2007)	Case-control study of 222 people who died by suicide between 1999 to 2000 whilst in psychiatric in-patient care in England and Wales. Previous deliberate self-harm (OR=4.3), recent adverse life events (OR=2), and symptoms of mental illness at last contact with staff (OR=2) were associated with increased risk for suicide.

Suicide and other causes of mortality in bipolar disorder: A longitudinal study (Dutta, Boydell et al. 2007)	Cohort study of 235 patients from South-East London with first diagnosis of bipolar disorder between 1965 to 1999. Found that suicide is significantly increased (SMR for suicide=9.8), but actual case fatality was not as high as previously seen in the literature. Alcohol abuse (HR=6.7) and deterioration in premorbid functioning (HR=5.2) were associated with increased risk of suicide.
Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's General Practice Research Database (Osborn, Levy et al. 2007)	Cohort study using a community sample of 46,136 people with SMI and 300,426 matched comparators from the General practice research database. Found high risk of cardiovascular disease (HR = 1.1 to 3.2), and stroke deaths (HR = 1.3 to 2.5) in people with SMI not explained by the presence of common risk factors including anti-psychotic drug use, smoking or social deprivation
Suicide in psychiatric in-patients in England, 1997 to 2003 (Kapur, Hunt et al. 2006)	Using data from the national confidential inquiry into suicide linked to HES to track trends in in-patient and post-discharge suicide between 1997 to 2003. Found a fall in rate of inpatient and post-discharge suicide over the study period.
Suicide in schizophrenia: findings from a national clinical survey (Hunt, Kapur et al. 2006)	Case control study in a national sample of completed suicides in the UK between 1996-2000. Found that patients with schizophrenia who committed suicide were more likely to be young, male, unemployed and from ethnic minority. There was a high likelihood of violent method of suicide in schizophrenia patients
Psychiatric disorders certified on death certificates in an English population (Goldacre, Duncan et al. 2006)	Cross-sectional study using death certificate data from Oxford and England to report trends in the recording of psychiatric diagnosis on the death certificates. Found that mortality associated with psychiatric illness is greatly under-estimated if only the underlying cause is taken into account. Also found that the trend in recording psychiatric diagnosis on the death certificates varies between disease over time, with a decline in mortality rates for schizophrenia, and an increase for depression and dementia recorded on death certificates between 1979 -1999.
Lifetime suicide rates in treated schizophrenia: 1875-1924 and 1994-1998 cohorts compared (Healy, Harris et al. 2006)	Small study using inpatient records linked to mortality data, comparing the suicide rates before and after introduction of chlorpromazine in North-West Wales. Found that suicide rates per hospital admission were twenty times higher between the first and last surveys
Suicide in schizophrenia: a retrospective case-control study of 51 suicides (Sinclair, Mullee et al. 2004)	Retrospective case control study of 51 schizophrenia patients and 82 matched controls in Wessex for factors associated with suicide. Found that depressive symptoms (OR=2.6) and previous suicide attempts (OR=2.7) are significant predictive factors.
Mortality after discharge from long-term psychiatric care in Scotland, 1977-94: a retrospective cohort study (Stark, MacLeod et al. 2003)	Cohort study of mortality trends in 6776 people discharged from long stay psychiatric in-patient care with SMI between 1977 to 1994 and followed up to 15 years. Found high SMRs = 1.6 for all-causes and for both natural and unnatural causes of death
Suicide following deliberate self-harm: long-term follow-up of patients who presented to a general hospital (Hawton, Zahl et al. 2003)	Prospective case register study of 11583 patients who had undertaken deliberate self-harm (DSH) between 1978 - 1997. Found that there was a significant and persistent risk of subsequent suicide, which varies by age and sex. RR of suicide in 1st year after episode of DSH = 66

Causes of the excess mortality of schizophrenia (Brown, Inskip et al. 2000)	Follow-up study of mortality in 370 schizophrenia patients in Southampton who used mental health services between 1981 - 1982. Used medical records linked to death certificates/ coroners records. Found high SMRs for both natural/ unnatural causes of death, especially for smoking related diseases

Studies have found that the overall mortality for these populations has been increasing over the last few decades in several countries (Saha, Chant et al. 2007; Lawrence, Kisely et al. 2010). At the same time other researchers have found a decreasing mortality trend, especially for deaths from unnatural causes or in people living in the community (Capasso, Lineberry et al. 2008; Pirkola, Sund et al. 2009; Rantanen, Koivisto et al. 2009), whilst others found no change in mortality (Desai and Rosenheck 2003; Heila, Haukka et al. 2005). However there were only four studies published in the last decade that also included data from 2000 in the UK, two of which focused on recent trends in mortality from suicide in people with SMI (Dutta, Murray et al. 2010; Hunt, Windfuhr et al. 2010), one studied all-cause mortality in people with SMI (Chang, Hayes et al. 2010) and finally one small study that tracked the trend in all-cause mortality rates for people with schizophrenia (Brown, Kim et al. 2010).

The differences in mortality between the community and inpatient or recently discharged samples emphasise that the period of acute illness and immediate community rehabilitation for these patient populations remains a time of high risk of death (Goldacre, Seagroatt et al. 1993), possibly increasingly so. As mentioned above this may be due to a number of reasons including;

- increasing investment in community mental health services and decreasing investment in inpatient services
- increasing concentration of the most sick clients in inpatient care, including people with physical comorbidities
- side-effects of modern anti-psychotics prescribed for acute and ongoing management of these clients
- difficulties accessing physical healthcare services or public health services for people recently discharged from inpatient care
- poor quality physical healthcare offered to people with physical health and severe mental health problems

Chapter 3 - Gaps in current research

The literature review revealed a number of significant gaps in the evidence base on mortality amongst people with bipolar disorder and schizophrenia.

First, there is little recent information about all-cause mortality in people with schizophrenia at a national level in the UK, with only two local studies reporting information on all-cause mortality rates in these people within the last decade (Brown, Kim et al. 2010; Chang, Hayes et al. 2010), and a further two national studies reporting on suicide outcomes only (Dutta, Murray et al. 2010; Hunt, Windfuhr et al. 2010).

Second, there is very little information on the mortality outcomes for people with bipolar disorder within the last decade in the UK. Only one article has reported all-cause mortality rates in these populations utilising data from 2000 onwards (Chang, Hayes et al. 2010), whilst the next most recent article reported on data collected between 1965-99 (Dutta, Boydell et al. 2007). This limits conclusions about the epidemiology of mortality for these populations in the UK as a whole, as the mortality risk is dependent upon the age of the population studied, the length of follow up and type of study used to measure the risk (Bushe, Taylor et al. 2010). As mentioned earlier, there is good evidence to suggest that the mortality risk in these populations will have changed over the last decade.

Third, there is little information on recent time trends in mortality for either population in the UK, with only one study that tracked the trend in all-cause mortality rates in these populations over the past decade (Brown, Kim et al. 2010). However systematic reviews collating information from other countries have suggested that these populations may not be benefiting from the decreasing mortality in the general population, resulting in a widening of the mortality gap (Saha, Chant et al. 2007; Lawrence, Kisely et al. 2010; Mitchell and Lord 2010). These deficits in information are particularly relevant to current mental health policy

which makes a specific commitment to tackling the well-known ‘mortality gap’ between people with mental disorders and the general population.

Fourth, there is little recent information on mortality in populations with schizophrenia or bipolar disorder who may be at greater risk of death in the UK including the elderly who are at risk of side-effects from anti-psychotics (Citrome 2007; Leon, Gerretsen et al. 2010), people who have difficulty accessing health services, such as those who live in rural areas or whose first language is not English, and people who present with comorbid physical illnesses. Evidence from Australia and elsewhere suggests that these people may also have additional risk above that experienced by people without these risk factors (Druss, Bradford et al. 2000; Druss, Bradford et al. 2001; Lawrence, Holman et al. 2003; Abrams, Vaughan-Sarrazin et al. 2008; Abrams, Vaughan-Sarrazin et al. 2009; Laursen, Munk-Olsen et al. 2009; Lawrence and Kisely 2010; Mitchell and Lord 2010). This information is relevant to better characterise mortality for these populations, to identify factors that may be of etiological importance, and to allow better targeting of interventions to reduce mortality.

Finally, whilst there is evidence that a proportion of excess mortality in these populations is the result of avoidable or modifiable conditions (Rasanen, Hakko et al. 2005; Amaddeo, Barbui et al. 2007; Wildgust and Beary 2010; Wildgust, Hodgson et al. 2010), there is little information to quantify the effect of these conditions within populations in the UK, or to evaluate interventions that could be used to reduce their effects. Knowledge of this information could help us better understand the nature of mortality in these populations as well as giving us information on what is possible with current interventions to reduce mortality.

Chapter 4 – Objectives and hypothesis

Thus in this thesis, I sought to investigate recent mortality trends in people with schizophrenia and bipolar disorder in England over the past decade, and seek to answer the following research questions;

1. Has the excess in all-cause mortality for people with bipolar disorder and schizophrenia increased or decreased over the last decade in England?
2. Is the mortality excess of the same magnitude for people with bipolar disorder and schizophrenia in England?
3. Is the trend in mortality consistent for people with bipolar disorder and schizophrenia of different ages and genders in England?
4. Is mortality for people with bipolar disorder and schizophrenia geographically consistent across England?
5. Does comorbid illness with bipolar disorder and schizophrenia in people with another main diagnosis, namely cardiovascular disease or diabetes, result in excess mortality?
6. To what extent are causes of excess deaths potentially avoidable in people with bipolar disorder and schizophrenia and therefore what would be the impact on the mortality excess of equalising those causes in England?

Objective 1

It is well known that people schizophrenia and bipolar disorder are at increased risk of death compared with the general population from all-causes (Allebeck 1989). However, less is known about current national trends in mortality, including whether the mortality gap has been reducing over the last decade in England. In fact as mentioned in the last chapter only one study from the UK gives mortality rates for bipolar disorder (Chang, Hayes et al. 2010) and only two give mortality rates for schizophrenia (Brown, Kim et al. 2010; Chang, Hayes et al. 2010) using data collected from local psychiatric registers over the last decade. None

provides enough information about national mortality trends for these populations in the last decade in England.

Saha and colleagues reviewed 37 studies from 25 countries looking at mortality in people with schizophrenia between and found that the mortality gap for all-causes had increased over the course of their study between 1980 – 2006 (Saha, Chant et al. 2007). However Saha did not include any studies conducted at a national level in the UK using data from the last decade.

Based on this evidence I hypothesised that the trend in all-cause mortality in these populations in England would have increased over the last decade, with a resultant increase in the mortality gap compared with the general population.

Objective 2

As explained earlier, schizophrenia and bipolar disorder share a number of features in common, including a high risk of mortality. Previous studies have compared the mortality gap in people with bipolar disorder and schizophrenia and found that people with schizophrenia had a greater mortality gap with the general population than people with bipolar disorder (Laursen, Munk-Olsen et al. 2007; Chang, Hayes et al. 2010). However no studies have compared the mortality gap for these populations more recently at a national level in England.

Thus based on previous evidence I hypothesised that the mortality gap for people with bipolar disorder, would be less than the gap seen in people with schizophrenia

Objective 3

Previous studies have shown that age is an important determinant of death in people with SMI, with the mortality gap greatest for the young compared with the elderly (Hawton, Zahl et al. 2003; Rasanen, Hakko et al. 2003; Hunt, Kapur et al. 2006; McGirr and Turecki 2008;

Reutfors, Brandt et al. 2009). In addition some studies have shown that gender is an important determinant of mortality, although the effect of gender on the mortality gap has not been consistent (Lawrence, Jablensky et al. 2000; Hansen, Fink et al. 2001; Joukamaa, Heliovaara et al. 2001; Osby, Brandt et al. 2001; Politi, Piccinelli et al. 2002; Lawrence, Holman et al. 2003; Limosin, Loze et al. 2007; Hiroeh, Kapur et al. 2008). Studies have suggested that deaths from suicide and other unnatural causes, common amongst the young is falling (Kapur, Hunt et al. 2006), indicating decreasing mortality amongst the young. However no studies have shown how age and sex affect recent trends in the mortality gap in England.

Given the current evidence of age effects on mortality, I hypothesised that the mortality gap for the young (<45 years) is narrowing and the mortality gap for others remains the same. Given the conflicting evidence of the gender effects on mortality, I hypothesised that there is no difference in trends in the mortality gap for different genders.

Objective 4

A recent study from Finland by Kiviniemi and colleagues has suggested that geographical location may be a determinant of mortality in people with SMI (Kiviniemi, Suvisaari et al. 2010), and evidence from local studies undertaken in the UK show variation in the mortality risk estimates calculated from different disease registers (Brown, Leith et al. 2010; Chang, Hayes et al. 2010). However these local studies are difficult to compare directly as they have different inclusion criteria and cover different time periods.

Given the lack of evidence on this subject, I hypothesised that there would be no difference in the magnitude of the mortality gap for people with bipolar disorder or schizophrenia over different geographical locations within the same time period.

Objective 5

Previous studies have shown that people with a physical illness and comorbid SMI including schizophrenia are at higher risk of death than those without comorbid SMI (Lawrence, Holman et al. 2000; Lawrence, Jablensky et al. 2000; Lesperance, Frasure-Smith et al. 2000; Jaffe, Krumholz et al. 2006; Lawrence and Kisely 2010). However other researchers have shown no such effect of comorbid SMI (Abrams, Vaughan-Sarrazin et al. 2008; Abrams, Vaughan-Sarrazin et al. 2009; Abrams, Vaughan-Sarrazin et al. 2010; Abrams, Vaughan-Sarrazin et al. 2010). Thus far no studies have been undertaken on this subject in the UK.

Given the conflicting evidence I hypothesised that there would be no difference in the magnitude of mortality risk for people with comorbid bipolar disorder and schizophrenia, who present to inpatient care with a main diagnosis of cardiovascular disease or diabetes, compared with those without comorbid mental disorder.

Objective 6

Avoidable causes of death have recently been estimated to account for 24% of all deaths in the general population in the UK (Wheller, Baker et al. 2007). This compares with 30% of all deaths in people with SMI in Finland (Rasanen, Hakko et al. 2003). No comparable recent data is available for people with SMI in the UK, however this data suggests that reducing the extent of avoidable deaths in the people with SMI would reduce the mortality gap, although no studies to date have quantified this.

Thus I hypothesised that, if causes of death, in people with bipolar disorder or schizophrenia, that are amenable to high quality medical care or preventable by access to public health intervention were reduced to levels expected in the general population in these groups, then the excess mortality could be eliminated entirely.

Chapter 5 – Methods

As shown in chapter 2, studies investigating mortality in people with SMI have previously utilised a number of observation research strategies, especially cohort and case-control study designs. Thus the main studies in this thesis cohort designs have been used to answer the research questions posed. The specific methods used to answer each research question, including the methods used to define cohorts, measure exposure, select important co-variates, and identify and analyse outcomes are outlined separately in each chapter.

Datasets used for this study

A linked dataset created by staff from the UHCE was used to examine the epidemiology of mortality within the last decade in England. This linked dataset contains 13 years of information from English national Hospital Episode Statistics (HES data, supplied by the NHS Information Centre) and death registrations (supplied by the Office for National Statistics) from 1st April 1998 to 31st March 2010. Further information regarding the dataset used is shown in Table 5-1 and details of the methods used to create this file are included in Appendix 3.

The hospital component of the dataset includes statistical abstracts of records of all inpatient admissions, including day cases, in NHS acute and psychiatric hospitals in England. Information about diagnoses is coded using the International Classification of Diseases (ICD) revision 10 (WHO). The hospital records of individual patients are stored as Finished Consultant Episodes (FCE), i.e. a period of admitted patient care under a consultant or allied healthcare professional within an NHS trust. Data linkage techniques allow FCEs to be grouped together into one record of a patient's entire inpatient stay, regardless of any inter-hospital transfers which may take place, known as a Continuous Inpatient Spell (CIP) (2006). A single CIP may contain information from one of more FCEs. Where a CIP consists of more than one FCE, information from the first FCE for that individual’s inpatient stay, including

details of the diagnosis made, is considered the 'admission record', and the last record is considered the 'discharge record'. The dataset containing CIP records was used for this study. CIP records will be described as 'hospital records' from this point forward. Data linkage facilitates the calculation of person based statistics.

In addition to hospital records, the linked dataset contains data derived from death certificates collected by the Office for National Statistics (ONS) that covers England (and Wales). This information includes the date of death and the causes of death which are coded using the International Classification of Diseases revisions 9 (covering the period between 1998–2000) and 10 (covering the period between 2001-2010). More information about the specific variables included in this dataset can be found in Table 5-2 and by reference to the HESOnline website (www.hesonline.nhs.uk).

Statistical analyses were performed with the SAS statistical software package (SAS Institute, 1992).

Comparison Group

In order to calculate the mortality gap for people with bipolar disorder or schizophrenia, the mortality rate prevailing in the general population of equivalent age and sex over the same time period was the comparison group used.

Consideration of the feasibility and anticipated limitations of the dataset and methods chosen in this study for answering the study objectives

As explained in the previous chapters, studies investigating mortality in SMI have used observational research methods, with the majority utilising a prospective cohort design. This involves the identification of a cohort of people with SMI from hospital records with follow-up undertaken by linking the patient's health records with their death records to identify study

outcomes. This is the method I propose to use to investigate mortality for people with bipolar disorder and schizophrenia in England, and is feasible with the national linked health records dataset described above.

However investigating the mortality gap and mortality trends for people with SMI using observational research methods and routinely collected data has a number of limitations which one should expect to encounter and which may affect the study results, or limit the conclusions that can be drawn from them (see Table 9-1). Although none of these limitations would compromise the feasibility of investigating mortality in people SMI proposed for this thesis.

First, the selection of cases is dependent on the inclusion of people with bipolar disorder and schizophrenia within the dataset. Given the management of people with SMI being increasingly moved to the outpatient and community setting (2000; 2001; Glover, Arts et al. 2006; Onyett, Linde et al. 2008), records that are not included in this dataset, the likelihood is that selection of cases will be biased towards those who have the most severe symptoms or are poorly managed in the community. The extent to which the study populations in this thesis represents all people with bipolar disorder and schizophrenia could be gauged by comparing with data from the mental health minimum dataset (MHMDS), which collates information from outpatient and community contacts or the General Practice Quality and Outcomes Framework (QOF) SMI registers which collects information from primary care. I have not undertaken these comparisons within this thesis, and would suggest that this is addressed in future research.

In addition, the follow-up of cases who have recently been discharged from inpatient care, a period of high mortality risk is also likely to influence the mortality risk estimates, as mentioned earlier. Whilst these factors may circumscribe the conclusions that can be drawn, they should not limit the ability to answer the research questions posed. I would suggest that future research possibly using other datasets such as the General Practice Research

Database (GPRD) or the QOF SMI register which may include people with SMI who have not recently attended inpatient care, or variables measuring disease severity may be conducted to provide different mortality risk estimates for a wider group of people in these populations and for a longer period of time in the community.

Second, the investigation of important explanatory or confounding factors is dependent on the recording of these variables in the dataset or else the use of a further dataset that could be easily linked to this dataset. Age, sex and geographical location are recorded on this dataset and can be examined to investigate their effect on mortality, namely in objectives 3 and 4. It also contains other variables which may be important in determining mortality such as a population level deprivation indicator, the Index of Multiple Deprivation (IMD) which assigns a score to each person based upon their postcode address. This variable was not used in this thesis. However the dataset does not include information on other important confounding or explanatory variables some of which are listed in Figure 1-1 such as mental illness severity, the presence of physical illness, smoking, alcohol/ substance abuse, access and quality of healthcare services, and the use of anti-psychotic medications. This may result in residual confounding and may limit the conclusions that can be drawn.

Methods using data from local psychiatric disease registers, such as the Clinical Record Interactive Search (CRIS) database held by the South London and Maudsley NHS Trust could provide information on some of these confounding and explanatory variables such as smoking status and use of anti-psychotic medications, however they cannot provide a nationally representative picture of mortality risks for these groups. Methods can also be used to link to information from national datasets such as the MHMDS (Glover 2007) or the NHS workforce statistics released by the NHS Information Centre which can provide important information on the provision of health services, however they are collected at the organisational level and like aggregate measures of deprivation such as the IMD are difficult to assign to individual records.

Third, the calculation of the mortality gap, a measure of relative risk, will also be influenced by the selection of the comparison group. In this thesis the mortality gap is the difference between the mortality rate in the populations recently discharged from hospital with SMI and the mortality rate prevailing in the general population of equivalent age and sex over the same time period. Both of these populations are resident in the community, and the assumption is that both are exposed to the same risk factors for mortality, with the only difference being a diagnosis of mental illness in our study groups. However as explained earlier the period following discharge for those with SMI is known to be a period of heightened risk of death which may reflect common risk factors around the management of hospital discharge and reintegration into the community that operate following hospital discharge and may not be present amongst other people within the community. Thus the use of mortality rates in other comparison populations, such as all people discharged from hospital, or all people with a diagnosis of mental illness, could possibly be used as comparison groups to calculate the mortality gap. Murray and colleagues have suggested that the population health effects of individual or groups of risk factors should be quantified by 'comparing the burden of disease due to the observed exposure distribution in a population with the burden from a hypothetical distribution or series of distributions, rather than a single reference level such as non-exposed' (Murray, Ezzati et al. 2003). This would involve the calculation of a range of values within which the true mortality gap lies and is not the approach I have taken in this thesis. However the methods I have used do provide one estimate of the mortality excess for these populations and can be added to by other researchers using different methods.

Fourth, prospective follow-up is undertaken in our studies by linking hospital records to outcomes data contained in death records. The completeness of follow-up is dependent on the quality and completeness of data-linkage between the hospital and death records. This in turn is dependent on the quality and completeness of recording of data variables used to undertake data linkage. Whilst changes in the recording of diagnosis, and variables used for data linkage may not affect studies done over a short period of time, studies done over

longer periods of time or looking at trends may be affected by changes in the recording of diagnosis and the quality of data linkage in routinely collected linked databases.

Table 5-1 shows that there were approximately 3.6 HES records per person in the 13 year linked dataset. This is higher than previously reported for a 4 year file covering the period from 1st April 1998 to 31st March 2002, which included 51,554,709 HES and death records for 22,672,262 people, equating to 2.3 HES and death records per person (Gill 2004). The same methods for linking have been used by staff at the UHCE over the intervening period and are described in Appendix 3 along with the methods used for data extraction. This discrepancy could be accounted for by changes in hospital discharge practices over the duration of the file, with earlier discharge of patients and more frequent readmissions or changes in the quality of data linkage between over the course of the 13 year file may also explain this discrepancy, this is suggested by the NHS Information Centre and HESOnline, which showed that the recording of valid NHS numbers on HES records increased from 83.2% in 2000-01 to 96.8% in 2008-09 (2009). This may result in more linked death records being identified towards the end of the datafile than at the start, and may cause an inflation of all post-discharge mortality rates. Equally, if more records were assigned to each person, namely more readmissions were identified then the counting methods used in this thesis, namely counting only the first admission in a study period and ceasing follow-up when there is a readmission for any diagnosis or death, (described more fully in chapter 6) would be expected to decrease the number of deaths included and deflate all post-discharge mortality rates. Changes in hospital admission practices for example more frequent use of outpatient or community care services for people with mental illness can be gauged from data submitted to the MHMDS, as described in chapter 6.

Table 5-1 - Number of hospital records included in the dataset* used for this study

	All records of admissions in England	England residents only (where country = 'E')
No. of hospital records for both sexes	134,476,138	132,737,995
No. of hospital records for men	63,967,187	63,112,842
No. of hospital records for women	70,438,868	69,559,825
No. of hospital records for unspecified sex	70,083	65,328
No. of people	37,409,481	36,397,787
No. of men	17,853,779	17,384,000
No. of women	19,485,619	18,948,460
No. of unspecified sex	70,083	65,328

* filename = cips_13yr_v06_newrt (13year cips file)

Table 5-2 - Variables in the UHCE CIPs dataset

Variable	Description
Sysno	UHCE ID key
SQLkey	UHCE ID key
Record	Record type; indicates whether the record is a death or hospital record
Recno	Record number
D1 to D7	For hospital records: Diagnostic codes used on the discharge hospital record. D1 is the main diagnosis on discharge. For this thesis the term 'main diagnosis' is used for the diagnostic code variable D1 on a hospital record For death records: Diagnostic codes used on the death certificate. D1 is the 'underlying' cause of death. D2 to D12 on death records are any other cause of death recorded on the death certificate
D8 to D14	Diagnostic codes used on the admission hospital record. D8 is the main diagnosis on admission on a hospital record
D15 to D18	Other diagnosis not mentioned on the admission or discharge on the hospital record
O1 to O12	Operative codes mentioned anywhere during the patient's inpatient stay (not used for this thesis)
Sex	Gender
Ethnos	Ethnicity
Resid	Area of residence
Treat	Area of Treatment
Spa	Specialty on admission
Spd	Specialty on discharge
dis	Disposal
sor	Source of admission
Daycase	Record from a daycase, yes or no
los	Length of stay in days
Age	Age
Daycase	Whether the patient was a daycase or not
Admyear	Year of admission
Admisorc	Admission source
Admimeth	Admission method
Finyear	Year of discharge
Disyear	Year of disposal
Dxed	Diagnosis edition
Oped	Operative edition
Numrecs	Record number
Jdoa	Date of admission
Jdod	Date of discharge
Deathdat	Date of death
Hosp	Hospital code
Trust	NHS Trust
Resgor	Government office region code
Country	Country

Ethical approval

The National Health Service Central Office for Research Ethics Committees approved the current work programme of analysis using the linked data sets held at the Unit of Health-Care Epidemiology (reference number 04/Q2006/176).

See Appendix 4.

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Chapter 6 – Recent trends in all-cause mortality following hospital discharge of with a main diagnosis of bipolar disorder or schizophrenia

Research questions

1. Has the excess in all-cause mortality for people with bipolar disorder and schizophrenia increased or decreased over the last decade in England?
2. Is the mortality excess of the same magnitude for people with bipolar disorder and schizophrenia in England?
3. Is the trend in mortality consistent for people with bipolar disorder and schizophrenia of different ages and genders in England?
4. Is mortality for people with bipolar disorder and schizophrenia geographically consistent across England?

Method

Study inclusion criteria

In order to examine the research questions posed in this chapter, all records of discharges from inpatient care in England between 1st January 1999 and 31st December 2006 with either bipolar affective disorder (ICD10 code F31) or schizophrenia (ICD10 codes F20 to F29) as the main diagnosis on the hospital discharge record were extracted. Cases that occurred after 1st January 2007 were not included as some specific mortality outcomes, such as reports of deaths from misadventure and suicide were incomplete towards the end of the 10 year data file used originally for this study. Note that the 10 year datafile contains information from 1st April 1998 until 31st March 2007, unlike the current 13 year file described in chapter 5 which contains information until 31st March 2010. This dataset was not available at the commencement of the thesis but is the same in every way apart from the additional 3 years data.

The first record in each study period with the diagnosis of interest was selected. Follow-up time was counted from the time of discharge from this first admission in the study period. Follow-up was ceased for the following reasons; 1) The patient died, 2) The patient was readmitted as an inpatient for any reason.

Thus for a patient who was admitted multiple times during the study period, then only the first admission with the diagnosis of interest would be counted, other readmissions in the study period would not be counted. Further information on about the data extraction methods used can be found in Appendix 3.

Outcomes

The primary outcome of the analysis in this chapter was all-cause mortality within 365 days following psychiatric inpatient care as defined above. As explained previously, the period immediately following hospital discharge is the period of highest risk of death and thus an *a priori* decision was made to focus on mortality outcomes in the first year after hospital discharge.

The relative contributions of unnatural and natural causes to all cause mortality was also studied. Unnatural deaths were defined on the basis of ICD10 codes V01 to Y98 or ICD9 codes E800 to E999 recorded anywhere on the death certificate; the remaining deaths were classified as natural.

In order to allow more detailed interpretation of deaths under these broad categories data for deaths from the following specific causes are also presented where there were sufficient deaths to provide a stable estimate of mortality risk, namely deaths from the following conditions;

- cardiovascular disease (ICD10 codes I00 to I99, ICD9 codes 390 to 459),
- respiratory disease (ICD10 codes J00 to J99, ICD9 codes 460 to 519),
- cancer (ICD10 codes C00 to D48, ICD9 codes 140 to 239),

- accidents (ICD10 codes V01 to X59, ICD9 codes E800 to E929)
- suicide/ deaths from undetermined intent (ICD10 codes X60 to X89 and Y10 to Y34, ICD9 codes E950 to E959 and E980 to E989).

Analysis

Number of discharges and discharge trend analysis

In order to comment on the trend in discharges from hospital for people with a main diagnosis of bipolar disorder and schizophrenia over the period of the study, the number of discharges was plotted over the course of the study and a line of best fit drawn to describe the trend in discharges. The slope of the line was calculated to quantify the direction and steepness of the trend. The R-square value was presented to show the proportion of the variance in the trend that could be explained by the line of best fit.

Calculating relative mortality rate

The mortality gap or the relative mortality rate in this chapter is conceptualised as the difference between the mortality rate in the populations recently discharged from hospital with SMI, and the mortality rate prevailing in the general population of equivalent age and sex over the same time period. Both of these populations are resident in the community, and the assumption is that both are exposed to the same risk factors for mortality, with the only difference being a diagnosis of mental illness in our study groups. In order to quantify the extent of excess deaths, mortality rates after hospital discharge as age and sex standardised mortality ratios were calculated, comparing mortality in the people with bipolar disorder or schizophrenia, with mortality in the general population of England at the same period of time. Standardisation was carried out using the indirect method, in five-year age groups, with the age- and sex-specific mortality rates of England in the same time periods as the standard. These age- and sex-specific rates were applied to the age and sex structure of each of the discharge cohorts with bipolar disorder or schizophrenia to calculate an 'expected' number of deaths. The observed number was compared with the expected number to calculate the

SMRs, with confidence intervals calculated as described elsewhere (Higham, Flowers et al. 2005).

Standardisation allowed an adjusted quantification of the absolute mortality rate for people with bipolar disorder or schizophrenia compared to the general population and also, because the reference group was the same for each condition, it permits comparisons between the two disorders.

Absolute mortality rate

Any change in relative mortality rates could represent an absolute rise in mortality rates in the case populations, or a fall in mortality rates in the general population in conjunction with a smaller fall in mortality rates in the psychiatric population. Accordingly, the absolute all-cause post-discharge death rates per 100,000 people discharged with bipolar disorder and schizophrenia were also calculated.

Sex-specific and age-truncated analysis

In order to comment on mortality for people with a main diagnosis of bipolar disorder and schizophrenia of different ages and different genders, separate analyses for males and females were undertaken, and age-truncated analysis using the following three broad groups selected *a priori*: working age young adults (< 45 years), middle aged adults (45 to 64 years), and older adults (65 to 84 years). Children equal to, or under 15 years were excluded, and data on people >85 years is not presented due to small numbers.

Geographical variations in mortality rates

In order to comment on the question of geographical variations in mortality, the SMRs for each regional health authority area were calculated separately, comparing mortality in people with bipolar disorder or schizophrenia admitted to inpatient care in each Regional Office (RO) area, using the configuration as of 2006, with the mortality rates in the general population of England as a whole, using the method described above.

Mortality excess trend analysis

In order to examine trends in excess mortality, SMRs for each annual discharge cohort were calculated, taking mortality in the general population during the year of discharge in question as the reference mortality rate. This analysis allows the variation in mortality excess over time to be analysed taking into account variations in the mortality rate of the general population over the same time period. The Poisson test of trend was used to test whether the trend in SMRs was a significant over time (Breslow and Day 1987).

Results

Total number of discharges with bipolar disorder and schizophrenia

This study included a total of 100,851 discharges from hospital with a main diagnosis of bipolar disorder; and 272,248 discharges with a main diagnosis of schizophrenia in England between 1999 and 2006. Table 6-1 and Table 6-2 show the basic demographic characteristics of the populations. Over the course of the study, the total number of discharges with a main diagnosis of bipolar disorder decreased by 3.9% (from 12,369 to 11,888) between 1999 and 2006. The total number of people with a main diagnosis of bipolar disorder decreased by 2.4% (from 9,312 to 9,086) during the same time period. For those with a main diagnosis of schizophrenia, the number of discharges decreased by 10.9% (from 35,348 to 31,486) between 1999 and 2006, whilst the number of people decreased by 10.7% (from 27,133 to 24,205) over the same period. The percentage of men discharged was substantially higher amongst people with a main diagnosis of schizophrenia than bipolar disorder, and the proportion of men increased for both disorders over the period of the study. The median age of the discharge cohorts also increased slightly for both conditions.

Table 6-1 and Table 6-2 shows that there were approximately 1.3 HES records per person where the main diagnosis was bipolar disorder or schizophrenia. This is lower than the ratio of all HES records per person of 3.6 shown in Table 5-1, although it is in line with recent data

showing that approximately 33% of psychiatric admissions between 2003-09 were readmissions (Barker, Taylor et al. 2011). The ratio of HES records to people is dependent on two factors;

Firstly the ratio is dependent on the hospital admission practices for the particular condition, and the balance between treatment in inpatient settings and other settings such as outpatients or community treatment teams. This can be checked against other datasets that collect information on hospital inpatient, outpatient and community care, so that the relative proportions of care undertaken in each setting can be gauged. In this case the mental health minimum dataset (MHMDS) which includes data about the treatment of people with mental illness in inpatient care, outpatient care and community treatment services.

Secondly as explained earlier, the ratio also depends on the quality and completeness of data linkage between HES records. The quality and completeness of these linkages can be checked against two sources, namely previously published data from the UHCE (Gill 2004) and published information from the NHS Information Centre and HESonline. The data linkage methods between HES-HES records share many similarities with HES-death record linkage, thus any discrepancies in the data linkage of HES records would also be expected to affect HES-death linkage.

Table 6-1 - Number of discharges in England between 1999 and 2006, and number of people discharged, with a main diagnosis of BIPOLAR DISORDER, and their characteristics

	Main discharge diagnosis of BIPOLAR DISORDER (International Classification of Diseases revision 10 code F31)			
Year of discharge	Number of discharges	Number of people discharged	Number of males (% of all discharges)	Median age at discharge (M/F)
1999	12,369	9,312	3,527 (37.9)	42/ 48
2000	12,285	9,217	3,492 (37.9)	42/ 48
2001	12,803	9,384	3,608 (38.4)	43/ 48
2002	13,153	9,612	3,747 (39.0)	43/ 48
2003	12,757	9,723	3,767 (38.7)	44/ 48
2004	13,221	10,102	3,993 (39.5)	43/ 48
2005	12,375	9,284	3,644 (39.3)	44/ 48
2006	11,888	9,086	3,599 (39.6)	44/ 48

Table 6-2 - Number of discharges in England between 1999 and 2006, and number of people discharged, with a main diagnosis of SCHIZOPHRENIA and their characteristics

Main discharge diagnosis of SCHIZOPHRENIA (International Classification of Diseases revision 10 codes F20 to F29)				
Year of discharge	Number of discharges	Number of people discharged	Number of males (% of all discharges)	Median age at discharge (M/F)
1999	35,348	27,133	15,784 (58.2)	34/ 44
2000	33,793	25,785	14,883 (57.7)	34/ 44
2001	34,478	25,870	15,204 (58.8)	35/ 44
2002	34,105	25,524	15,290 (59.9)	35/ 44
2003	33,665	25,856	15,580 (60.3)	35/ 44
2004	35,540	27,425	16,428 (59.9)	35/ 44
2005	33,833	25,709	15,421 (60.0)	36/ 44
2006	31,486	24,205	14,829 (61.3)	36/ 44

Geographic variations in the number of discharges and trend in admissions for bipolar disorder and schizophrenia

The regional patterns of discharge for these two conditions in 2006 showed that London had the highest number of discharges for both conditions; 1,978 discharges with a main diagnosis of bipolar disorder for 1,526 people; and 7,155 discharges with a main diagnosis of schizophrenia for 5,646. The North East region had the lowest number of discharges for both conditions; 832 discharges with a main diagnosis of bipolar disorder for 667 people; and 1,647 discharges with a main diagnosis of schizophrenia for 1,297 people (see Table 6-3 and Table 6-4).

Plotting the trend in discharges for people with both conditions showed that the number of discharges had fallen for both bipolar disorder and schizophrenia in England between 1999 and 2006, with a relatively steeper decline for discharges with schizophrenia. The slope of the line of best fit suggests that there were 286.8 fewer discharges with a main diagnosis of schizophrenia per year compared with bipolar disorder which saw a modest reduction of 24.5 discharges per year over the study period, although the direct comparison of discharge trends in these two conditions is difficult as the slope of the line of best fit does not take into account the differences in the population size, the total number of discharges, the age/ sex compositions of discharges cohorts with the two conditions and the change in these factors over time.

Given the above provisos about the use of the lines of best fit to compare different samples, some general points will be made about the variation of discharge trends across the country. Table 6-3 and Table 6-4 show that most regions saw a decline in discharges over the study period, with the South West region seeing the greatest decrease in the number of discharges with a main diagnosis of bipolar disorder with 46 less discharges per year and the North West had the greatest decrease in the number of discharges with a main diagnosis of schizophrenia with 161 less discharges per year. In contrast, London saw substantial increases in discharges for both conditions over the study period. For bipolar disorder

London saw an increase of 59 discharges per year and, for schizophrenia, London saw an increase of 178 discharges per year.

Table 6-3 and Table 6-4 also shows that the ratio of HES records to people for each Regional Office varied between 1.2 to1.5 for both conditions, with no substantial variation between each area. This compares to a ratio of 1.3 for the UK as a whole.

Table 6-3 - Number of discharges (and number of people discharged), with a main diagnosis of BIPOLAR DISORDER, by Regional Office area and slope of the trend in the number of discharges

Regional Office area (RO)	Number of discharges (and number of people discharged), with a main diagnosis of BIPOLAR DISORDER								Slope of best fit line for discharges (R^2)
	1999	2000	2001	2002	2003	2004	2005	2006	
North East	735	685	804	687	807	835	631	832	7.4
	(572)	(525)	(599)	(511)	(593)	(616)	(485)	(667)	(0.1)
North West	1,927	1,916	2,131	2,151	2,032	1,981	1,902	1,774	-20.4
	(1,462)	(1,448)	(1,572)	(1,597)	(1,533)	(1,518)	(1,352)	(1,378)	(0.2)
Yorkshire & Humber	1,219	1,305	1,372	1,405	1,368	1,273	1,198	1,239	-8.7
	(894)	(993)	(1,049)	(1,028)	(1,033)	(983)	(917)	(939)	(0.1)
East Midlands	967	935	960	1,107	980	1,021	913	896	-6.6
	(697)	(708)	(682)	(782)	(721)	(762)	(701)	(687)	(0.1)
West Midlands	1,237	1,307	1,359	1,450	1,453	1,519	1,247	1,270	4.9
	(967)	(1,013)	(1,010)	(1,040)	(1,071)	(1,107)	(966)	(1,004)	(0)
East of England	1,301	1,156	1,125	1,199	1,022	1,227	1,205	1,080	-14
	(1004)	(863)	(888)	(882)	(803)	(944)	(887)	(830)	(0.2)
London	1,901	1,738	1,739	1,881	2,031	2,416	2,188	1,978	59.2
	(1,466)	(1,370)	(1,406)	(1,458)	(1,657)	(1,915)	(1,666)	(1,526)	(0)
South East	1,754	2,013	2,159	2,079	1,939	1,811	2,019	1,914	-0.40
	(1,325)	(1,400)	(1,383)	(1,490)	(1,474)	(1,405)	(1,531)	(1,444)	(0)
South West	1,328	1,230	1,154	1,194	1,125	1,138	1,072	905	-46.0
	(925)	(897)	(795)	(824)	(838)	(852)	(779)	(611)	(0.8)
Total England	12,369	12,285	12,803	13,153	12,757	13,221	12,375	11,888	-24.5
	(9,312)	(9,217)	(9,384)	(9,612)	(9,723)	(10,102)	(9,284)	(9,086)	(0)

Table 6-4 - Number of discharges (and number of people discharged), with a main diagnosis of SCHIZOPHRENIA, by Regional Office area and slope of the trend in the number of discharges

Regional Office area (RO)	Number of discharges (and number of people discharged), with a main diagnosis of SCHIZOPHRENIA								Slope of best fit line for discharges (R^2)
	1999	2000	2001	2002	2003	2004	2005	2006	
North East	1,910 (1,409)	1,719 (1,288)	1,949 (1,404)	1,563 (1,137)	1,708 (1,226)	1,629 (1,227)	1,450 (1,150)	1,647 (1,297)	-47.6 (0.5)
North West	6,141 (4,718)	5,609 (4,393)	5,988 (4,538)	5,655 (4,322)	5,441 (4,226)	5,488 (4,217)	5,186 (3,809)	4,751 (3,671)	-161.4 (0.8)
Yorkshire &Humber	3,255 (2,431)	3,320 (2,548)	3,550 (2,709)	3,812 (2,837)	3,642 (2,685)	3,471 (2,572)	3,278 (2,487)	3,316 (2,509)	-2.3 (0)
East Midlands	2,922 (2,122)	2,862 (2,113)	2,903 (2,016)	3,188 (2,180)	3,068 (2,213)	2,743 (2,028)	2,710 (2,014)	2,682 (2,034)	-36.2 (0.3)
West Midlands	3,155 (2,513)	3,179 (2,444)	3,157 (2,431)	3,311 (2,462)	3,135 (2,498)	3,572 (2,770)	3,010 (2,450)	2,991 (2,422)	-11 (0)
East of England	2,839 (2,248)	2,493 (2,015)	2,490 (1,971)	2,567 (1,929)	2,082 (1,672)	2,520 (1,983)	2,712 (2,054)	2,319 (1,781)	-35 (0.1)
London	7,040 (5,612)	6,377 (5,094)	6,274 (5,110)	6,338 (5,084)	7,022 (5,675)	8,442 (6,798)	7,769 (6,251)	7,155 (5,646)	178.0 (0.3)
South East	4,519 (3,479)	5,055 (3,543)	4,974 (3,350)	4,318 (3,221)	4,460 (3,396)	4,641 (3,587)	4,690 (3,208)	4,160 (3,033)	-61.8 (0.2)
South West	3,567 (2,601)	3,179 (2,347)	3,193 (2,341)	3,353 (2,352)	3,107 (2,265)	3,034 (2,243)	3,028 (2,282)	2,465 (1,812)	-109.4 (0.7)
Total England	35,348 (27,133)	33,793 (25,785)	34,478 (25,870)	34,105 (25,524)	33,665 (25,856)	35,540 (27,425)	33,833 (25,709)	31,486 (24,205)	-286.78 (0.3)

Death 365 days following discharge with a diagnosis of bipolar disorder or schizophrenia

Turning to mortality outcomes, approximately 1% of all discharges with a main diagnosis of bipolar disorder and schizophrenia were followed by mortality within one year over the course of the study. The proportion of deaths from natural and unnatural causes remained fairly consistent with about three in four of the deaths in each of the two cohorts due to natural causes (see Table 6-5 and Table 6-6).

Table 6-5 - Number of deaths from all-causes and unnatural causes in people discharged, with a main diagnosis of BIPOLAR DISORDER, in England between 1999 and 2006

	Main discharge diagnosis of BIPOLAR DISORDER (International Classification of Diseases revision 10 code F31)	
Year of discharge	Deaths from all causes within 365 days of inpatient discharge	Unnatural deaths within 365 days of inpatient discharge (% of all deaths)
1999	132	30 (22.7%)
2000	132	35 (26.5%)
2001	143	40 (27.9%)
2002	161	38 (23.6%)
2003	175	46 (26.3%)
2004	158	51 (32.3%)
2005	156	43 (27.6%)
2006	148	38 (25.7%)

Table 6-6 - Number of deaths from all-causes and unnatural causes in people discharged, with a main diagnosis of SCHIZOPHRENIA, in England between 1999 and 2006

	Main discharge diagnosis of SCHIZOPHRENIA (International Classification of Diseases revision 10 codes F20 to F29)	
Year of discharge	Deaths from all causes within 365 days of inpatient discharge	Unnatural deaths within 365 days of inpatient discharge (% of all deaths)
1999	416	114 (27.4%)
2000	427	113 (26.5%)
2001	408	111 (27.2%)
2002	389	86 (22.1%)
2003	459	106 (23.1%)
2004	429	123 (28.7%)
2005	414	112 (27.1%)
2006	376	96 (25.5%)

SMRs from all-causes

After taking account of the mortality rate in the general population over the same period of time, age and sex-standardised mortality ratios showed that mortality in the psychiatric cohorts was about double the population average. All-cause SMRs were 1.9 in people discharged with a main diagnosis of bipolar disorder in 2006, and 2.2 in people discharged with a main diagnosis of schizophrenia.

All-cause age-truncated and sex specific SMRs

For both sexes, SMRs were higher in younger than in older people (see Table 6-7). For example, in people discharged in 2006.

- Aged under 45 years, SMRs were 3.4 (95% CI: 1.7 to 5.1) for people with a main diagnosis of bipolar disorder and 6.2 (95% CI: 4.9 to 7.5) for people with a main diagnosis of schizophrenia.
- Aged 45 to 64 years, SMRs were 2.6 (95% CI: 1.8 to 3.4) for people with a main diagnosis of bipolar disorder and 3.9 (95% CI: 3.1 to 4.6) for people with a main diagnosis of schizophrenia.
- Aged 65 to 84 years , SMRs were 1.8 (95% CI: 1.4 to 2.2) for people with a main diagnosis of bipolar disorder and 2.0 (95% CI: 1.7 to 2.3) for people with a main diagnosis of schizophrenia.

Table 6-7 - All-cause post-discharge SMRs following hospital discharge in 2006

	All-cause SMRs 365-days following hospital discharge in 2006, for both sexes			
Main diagnosis on discharge	All ages	< 45 yrs	45-64 yrs	65-84 yrs
BIPOLAR DISORDER	1.9	3.4	2.6	1.8
SCHIZOPHRENIA	2.2	6.2	3.9	2.0

There was no significant gender difference in mortality for people discharged with a main diagnosis of bipolar disorder. For example, the SMRs for men discharged with a main diagnosis of bipolar disorder in 2006 was 2.3 (95% CI: 1.8 to 2.9) compared with 1.8 (95% CI: 1.4 to 2.2) for women.

Men discharged with a main diagnosis of schizophrenia had a significantly higher SMR within the first year than women, as shown from the fact that the confidence intervals for the SMRs in both sexes did not overlap, although formal significance testing was not undertaken. For example the SMRs for men discharged with a main diagnosis of schizophrenia in 2006 was 3.2 (95% CI: 2.8 to 3.6) compared with 1.8 (95% CI: 1.5 to 2.1) for women.

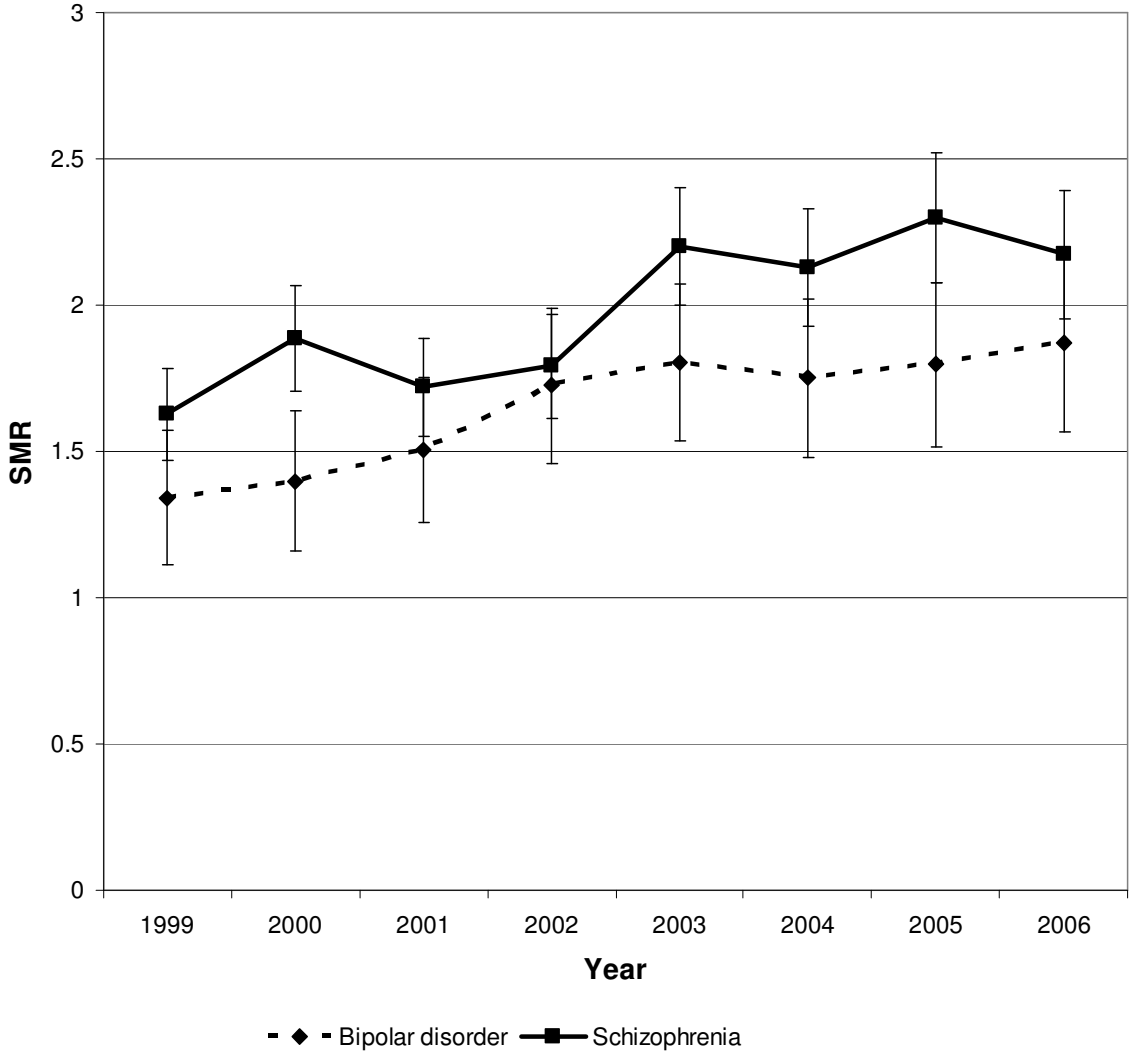
Trend in SMR from all-causes

As shown in Table 6-8 and Figure 6-1, SMRs for people with a main diagnosis of bipolar disorder increased from 1.3 (95% CI: 1.1 to 1.6) in people discharged in 1999 to 1.9 (95% CI: 1.6 to 2.2) in people discharged in 2006. The Poisson test of trend, between 1999 and 2006, was at borderline statistical significance (P=0.1). For people with a main diagnosis of schizophrenia, SMRs increased from 1.6 (95% CI: 1.5 to 1.8) in people discharged in 1999 to 2.2 (95% CI: 2.0 to 2.4) in people discharged in 2006, and the Poisson test of trend over this period was strongly significant (P<0.001).

Table 6-8 – Trend in all-cause post-discharge SMRs between 1999-2006 for BIPOLAR DISORDER AND SCHIZOPHRENIA, both sexes, all ages

	All-cause SMRs 365-days following hospital discharge	
Year of discharge	Main diagnosis of BIPOLAR DISORDER	Main diagnosis of SCHIZOPHRENIA
1999	1.3	1.6
2000	1.4	1.9
2001	1.5	1.7
2002	1.7	1.8
2003	1.8	2.2
2004	1.8	2.1
2005	1.8	2.3
2006	1.9	2.2
p-value for trend	*0.1*	*<0.001*

Figure 6-1 - Trend in all-cause SMRs 365-days following discharge for all people discharged from hospital with a main diagnosis of BIPOLAR DISORDER or SCHIZOPHRENIA



Trend in all-cause age-truncated SMRs

The trend in SMRs varied by age and sex. Whilst the SMRs were higher for younger than older populations there was no significant trend in SMRs for people under 45 years of age discharged with either diagnosis during the course of the study. In contrast, there was a noticeable upward trend for people aged 65 to 84 years discharged with either diagnosis during the course of the study.

For people with a main diagnosis of bipolar disorder aged under 45 years, the SMR decreased from 4.0 (95% CI: 2.0 to 6.0) in people discharged in 1999 to 3.4 (95% CI: 1.7 to 5.1) in people discharged in 2006. The Poisson test of trend, between 1999 and 2006, was not significant (P=1.0).

For people with a main diagnosis of bipolar disorder aged 45-64 years, the SMR increased from 1.7 (95% CI: 1.1 to 2.3) in people discharged in 1999 to 2.6 (95% CI: 1.8 to 3.4) in people discharged in 2006. The Poisson test of trend, between 1999 and 2006, was again not significant (P=0.8).

For people with a main diagnosis of bipolar disorder aged 65 to 84 years the SMR increased from 1.1 (95% CI: 0.9 to 1.4) in people discharged in 1999 to 1.8 (95% CI: 1.4 to 2.2) in people discharged in 2006. The Poisson test of trend, between 1999 and 2006, was not significant (P=0.2).

See Table 6-9.

Table 6-9 – Trend in all-cause post-discharge SMRs for BIPOLAR DISORDER between 1999-2006, both sexes, by age

	All-cause SMRs 365-days following hospital discharge with a main diagnosis of BIPOLAR DISORDER			
Year of discharge	All ages	< 45 yrs	45-64 yrs	65-84 yrs
1999	1.3 (1.1-1.6)	4.0 (2.1-6.0)	1.7 (1.1-2.3)	1.1 (0.9-1.4)
2000	1.4 (1.2-1.6)	3.9 (2.0-5.8)	2.3 (1.6-3.0)	1.3 (1.0-1.6)
2001	1.5 (1.3-1.8)	5.2 (3.0-7.3)	2.2 (1.5-2.8)	1.3 (1.0-1.6)
2002	1.7 (1.5-2.0)	4.6 (2.6-6.6)	2.7 (1.9-3.4)	1.6 (1.3-1.9)
2003	1.8 (1.5-2.1)	5.4 (3.2-7.5)	2.6 (1.8-3.3)	1.6 (1.3-1.9)
2004	1.8 (1.5-2.0)	8.0 (5.4-10.7)	2.7 (1.9-3.4)	1.4 (1.0-1.7)
2005	1.8 (1.5-2.1)	4.4 (2.3-6.5)	2.6 (1.8-3.4)	1.7 (1.3-2.0)
2006	1.9 (1.6-2.2)	3.4 (1.7-5.1)	2.6 (1.8-3.4)	1.8 (1.4-2.2)
p-value for trend	*0.1*	*1.0*	*0.8*	*0.2*

For people with a main diagnosis of schizophrenia aged under 45 years the SMR decreased from 6.9 (95% CI: 5.5 to 8.2) in people discharged in 1999 to 6.2 (95% CI: 4.9 to 7.5) in people discharged in 2006. The Poisson test of trend, between 1999 and 2006, was not significant (P=1.0).

For people with a main diagnosis of schizophrenia aged 45 to 64 years the SMR increased from 3.4 (95% CI: 2.8 to 4.0) in people discharged in 1999 to 3.9 (95% CI: 3.1 to 4.6) in people discharged in 2006. The Poisson test of trend, between 1999 and 2006, was not significant (P=1.0).

For people with a main diagnosis of schizophrenia aged 65 to 84 years the SMR increased from 1.3 (95% CI: 1.1 to 1.5) in people discharged in 1999 to 2.0 (95% CI: 1.7 to 2.3) in people discharged in 2006. The Poisson test of trend, between 1999 and 2006, was borderline statistically significant (P=0.05).

See Table 6-10.

Table 6-10 - Trend in all-cause post-discharge SMRs for SCHIZOPHRENIA between 1999-2006, both sexes, by age

	All-cause SMRs 365-days following hospital discharge with a main diagnosis of SCHIZOPHRENIA			
Year of discharge	All ages	< 45 yrs	45-64 yrs	65-84 yrs
1999	1.6 (1.5-1.8)	6.9 (5.5-8.2)	3.4 (2.8-4.0)	1.3 (1.1-1.5)
2000	1.9 (1.7-2.1)	7.5 (6.0-8.9)	3.5 (2.8-4.1)	1.7 (1.5-2.0)
2001	1.7 (1.6-1.9)	6.5 (5.2-7.8)	3.4 (2.7-4.0)	1.7 (1.4-1.9)
2002	1.8 (1.6-2.0)	6.2 (4.9-7.5)	3.3 (2.7-3.9)	1.6 (1.3-1.8)
2003	2.2 (2.0-2.4)	6.7 (5.4-8.1)	4.3 (3.5-5.0)	2.0 (1.7-2.2)
2004	2.1 (1.9-2.3)	7.5 (6.1-8.9)	3.6 (3.0-4.3)	1.8 (1.5-2.0)
2005	2.3 (2.1-2.5)	9.1 (7.4-10.7)	3.5 (2.8-4.1)	1.9 (1.6-2.2)
2006	2.2 (2.0-2.4)	6.2 (4.9-7.5)	3.9 (3.1-4.6)	2.0 (1.7-2.3)
p-value for trend	*<0.0001*	*1.0*	*1.0*	*0.05*

Trend in all-cause sex-specific SMRs

The SMRs for men were higher than women for both mental disorder cohorts, and there was no evidence of a narrowing of the gender differences in mortality during the study.

As outlined above, for bipolar disorder, there was no significant gender difference in mortality over the course of the study, with men who were discharged with a main diagnosis of bipolar disorder in 1999 having an SMR of 1.7 (95% CI: 1.2 to 2.1) which increased to 2.3 (95% CI: 1.8 to 2.9) in 2006, for which the Poisson test of trend, between 1999 and 2006, was not significant (P=0.9).

In comparison, for women discharged with a main diagnosis of bipolar disorder, the SMR was 1.4 (95% CI: 1.1 to 1.7) in women discharged in 1999 and had reached the same level as men at 1.8 (95% CI: 1.4 to 2.2) in people discharged in 2006, for which the Poisson test of trend, between 1999 and 2006, was not significant (P=0.4).

See Table 6-11.

Table 6-11 - Trend in all-cause post-discharge SMRs for BIPOLAR DISORDER between 1999-2006, all ages, by sex

	All-cause SMRs 365-days following hospital discharge with a main diagnosis of BIPOLAR DISORDER, by sex	
Year of discharge	MALE	FEMALE
1999	1.7	1.4
2000	1.8	1.5
2001	1.9	1.6
2002	2.1	1.8
2003	2.1	1.9
2004	2.3	1.6
2005	2.0	1.9
2006	2.3	1.8
p-value for trend	*0.9*	*0.4*

For men discharged with a main diagnosis of schizophrenia in 1999, the SMR was 2.3 (95% CI: 2.0 to 2.6) and increased to 3.2 (95% CI: 2.8 to 3.6) in men discharged in 2006. The Poisson test of trend, between 1999 and 2006, was statistically significant (P=0.04).

For women, the SMR increased from 1.6 (95% CI: 1.4 to 1.8) in women discharged in 1999 to 1.8 (95% CI: 1.5 to 2.1) in people discharged in 2006. The Poisson test of trend, between 1999 and 2006, was not significant (P=0.8).

See Table 6-12.

Table 6-12 - Trend in all-cause post-discharge SMRs for SCHIZOPHRENIA between 1999-2006, all ages, by sex

	All-cause SMRs 365-days following hospital discharge with a main diagnosis of SCHIZOPHRENIA, by sex	
Year of discharge	MALE	FEMALE
1999	2.3	1.6
2000	2.6	1.9
2001	2.5	1.7
2002	2.5	1.7
2003	2.9	2.0
2004	3.0	1.8
2005	3.3	1.9
2006	3.2	1.8
p-value for trend	*0.04*	*0.8*

SMRs for unnatural and natural causes

SMRs were highest for unnatural causes of death compared with natural causes. For example SMRs for unnatural death in people discharged with a main diagnosis of bipolar disorder in 2006 was 12.6 compared with 1.4 for natural deaths. Equally large differences in SMRs for unnatural and natural causes of death were seen in people discharged with a diagnosis of schizophrenia, (see Table 6-13).

Table 6-13 - SMRs for unnatural and natural causes of death 365-days following hospital discharge in 2006, both sexes

	SMRs for UNNATURAL causes			
Main diagnosis on discharge	All ages	< 45 yrs	45-64 yrs	65-84 yrs
BIPOLAR DISORDER	12.6	13.8	15.4	10.5
SCHIZOPHRENIA	11.6	15.2	14.3	6.5

	SMRs for NATURAL causes			
Main diagnosis on discharge	All ages	< 45 yrs	45-64 yrs	65-84 yrs
BIPOLAR DISORDER	1.4	0.3	1.8	1.6
SCHIZOPHRENIA	1.7	2.7	3.2	1.8

Trend in SMRs for unnatural causes

Trend analysis showed that there was no evidence of a narrowing mortality gap for unnatural causes. In people of all ages discharged with a main diagnosis of bipolar disorder, SMRs for unnatural causes were 9.3 (95% CI: 6.0 to 12.7) in 1999 and 12.6 (95% CI: 8.6 to 16.6) in 2006. The Poisson test of trend, between 1999 and 2006 was not significant, P=0.8 (see Table 6-14).

Table 6-14 - Unnatural cause post-discharge SMRs for BIPOLAR DISORDER, both sexes combined

	SMRs for unnatural causes 365-days following hospital discharge with a main diagnosis of BIPOLAR DISORDER			
Year of discharge	All ages	< 45 yrs	45-64 yrs	65-84 yrs
1999	9.3	10.6	10.6	6.5
2000	11.0	9.4	17.6	9.5
2001	12.3	14.1	18.7	6.6
2002	11.9	11.2	21.2	4.2
2003	13.9	17.2	13.0	15.1
2004	15.6	22.3	18.9	7.1
2005	14.2	11.5	27.5	7.5
2006	12.6	13.8	15.4	10.5
p-value for trend	*0.8*	*0.9*	*1.0*	*1.0*

The corresponding SMRs for people of all ages discharged with a main diagnosis of schizophrenia-associated was 11.6 (95% CI: 9.5 to 13.7) for people discharged in 1999 and 11.6 (95% CI: 9.3 to 13.9) in people discharged in 2006. The Poisson test of trend, between 1999 and 2006, was not significant (P=1.0). Numbers in individual age groups were small but there was no evidence of a narrowing of the gap in any age stratum (see Table 6-15).

Table 6-15 - Unnatural cause post-discharge SMRs for SCHIZOPHRENIA, both sexes combined

	SMRs for unnatural causes 365-days following hospital discharge with a main diagnosis of SCHIZOPHRENIA			
Year of discharge	All ages	< 45 yrs	45-64 yrs	65-84 yrs
1999	11.6	15.2	16.0	3.9
2000	12.3	16.7	12.2	8.7
2001	11.6	15.0	16.6	7.3
2002	9.8	13.0	10.0	7.9
2003	11.9	14.8	15.2	9.9
2004	13.6	17.9	18.1	4.8
2005	13.8	19.3	13.1	8.2
2006	11.6	15.2	14.3	6.5
p-value for trend	*1.0*	*1.0*	*1.0*	*1.0*

Trend in SMRs for natural causes

For natural causes, the mortality gap widened indicating that the increase in all-cause SMRs described earlier was accounted for principally by increases in natural causes of death. For people discharged with a main diagnosis of bipolar disorder of all ages, the SMRs was 1.2 (95% CI: 1.0 to 1.4) and 1.6 (95% CI: 1.3 to 1.9). Poisson test of trend, between 1999 and 2006, was not significant (P=0.3).

See Table 6-16.

Table 6-16 - Natural cause post-discharge SMRs for BIPOLAR DISORDER, both sexes combined

	SMRs for natural causes 365-days following hospital discharge with a main diagnosis of BIPOLAR DISORDER			
Year of discharge	All ages	< 45 yrs	45-64 yrs	65-84 yrs
1999	1.1	1.0	1.3	1.1
2000	1.1	1.4	1.5	1.1
2001	1.1	1.3	1.3	1.2
2002	1.4	2.0	1.7	1.5
2003	1.4	0.7	2.0	1.4
2004	1.2	2.3	1.8	1.3
2005	1.4	1.8	1.2	1.6
2006	1.4	0.3	1.8	1.6
p-value for trend	*0.3*	*1.0*	*1.0*	*0.3*

The corresponding SMRs for people of all ages discharged with a main diagnosis of schizophrenia was 1.3 (95% CI: 1.2 to 1.4) in people discharged in 1999 and 1.8 (95% CI: 1.6 to 2.0) in people discharged in 2006. Poisson test of trend, between 1999 and 2006, was highly significant (P=0.0001).

See Table 6-17.

Table 6-17 – Natural cause post-discharge SMRs for SCHIZOPHRENIA, both sexes combined

	SMRs for natural causes 365-days following hospital discharge with a main diagnosis of SCHIZOPHRENIA			
Year of discharge	All ages	< 45 yrs	45-64 yrs	65-84 yrs
1999	1.2	2.3	2.7	1.3
2000	1.5	2.6	3.0	1.6
2001	1.3	2.2	2.7	1.6
2002	1.5	2.9	2.9	1.5
2003	1.8	2.9	3.7	1.8
2004	1.6	2.7	2.8	1.7
2005	1.8	4.6	2.9	1.8
2006	1.7	2.7	3.2	1.8
p-value for trend	*0.0001*	*0.9*	*1.0*	*0.1*

SMRs for specific causes of death

Table 6-18 shows that deaths from accidents and from suicide/ undetermined intent in these populations exhibit the greatest disparity compared with general population rates. For example SMRs for accidental death in people discharged in 2006 were 6.6 and 6.3 for people discharged with a main diagnosis of bipolar disorder and schizophrenia respectively. For suicide and undetermined deaths the SMRs were higher at 19.8 and 20.9 for people with a main discharge diagnosis of bipolar disorder and schizophrenia respectively.

Table 6-18 - Specific cause post-discharge SMRs following hospital discharge in 2006, both sexes combined

	SMRs for specific causes 365-days following hospital discharge in 2006				
Main diagnosis on discharge	Circulatory disease (ICD10: I00-I99, ICD9: 390-459)	Cancer (ICD10: C00-D48, ICD9: 140-239)	Respiratory Disease (ICD10: J00-99, ICD9: 460-519)	Accidents (ICD10: V01-X59, ICD9: E800-E929)	Suicide and undetermined intent (ICD10: X60-X84, Y10-Y34, ICD9: E950-E959, E980-E989)
BIPOLAR DISORDER	2.5	0.6	5.8	6.6	19.8
SCHIZOPHRENIA	2.5	1.3	4.7	6.3	20.9

Trend in SMRs for specific causes of death

The trend analysis showed that whilst accidental deaths and suicide had the highest SMRs, the majority of the observed increase in the all-cause SMRs was accounted for by increases in mortality from cardiovascular and respiratory diseases.

For example, in people discharged with a main diagnosis of bipolar disorder the SMRs for circulatory disease increased from 1.6 (95% CI: 1.2 - 2.0) in 1999 to 2.5 (95% CI: 1.9 - 3.1) in 2006 (Poisson test of trend, between 1999 and 2006: P=0.2), whilst the SMRs for respiratory disease increased from 3.0 (95% CI: 2.1 - 3.8) in 1999 to 5.8 (95% CI: 4.3 - 7.3) in 2006 (Poisson test of trend, between 1999 and 2006: P=0.004).

See Table 6-19.

Table 6-19 - Specific cause post-discharge SMRs for BIPOLAR DISORDER, both sexes combined

Year of discharge	SMRs for specific causes 365-days following hospital discharge with a main diagnosis of BIPOLAR DISORDER				
	Circulatory disease (ICD10: I00-I99, ICD9: 390-459)	Cancer (ICD10: C00-D48, ICD9: 140-239)	Respiratory Disease (ICD10: J00-99, ICD9: 460-519)	Accidents (ICD10: V01-X59, ICD9: E800-E929)	Suicide and undetermined intent (ICD10: X60-X84, Y10-Y34, ICD9: E950-E959, E980-E989)
1999	1.6	0.4	3.0	6.8	13.5
2000	1.4	0.7	2.5	5.2	21.2
2001	1.6	0.5	3.7	4.7	24.8
2002	1.8	0.8	5.7	4.9	20.2
2003	1.8	0.9	5.0	4.0	27.7
2004	1.8	0.5	4.9	4.8	32.1
2005	2.1	0.6	4.6	5.0	29.5
2006	2.5	0.6	5.8	6.6	19.8
p-value for trend	*0.2*	*1.0*	*0.004*	*1.0*	*0.7*

For people discharged with a main diagnosis of schizophrenia, the SMR for circulatory disease rose from 1.6 (95% CI: 1.4 - 1.9) in 1999 to 2.5 (95% CI: 2.1 - 2.9) in 2006 (Poisson test of trend, between 1999 and 2006: P=0.0005), whilst the SMR for respiratory disease increased from 3.1 (95% CI: 2.6 - 3.6) in 1999 to 4.7 (95% CI: 3.8 - 5.6) in 2006 (Poisson test of trend, between 1999 and 2006: P=<0.0001).

See Table 6-20.

Table 6-20 - Specific cause post-discharge SMRs for SCHIZOPHRENIA, both sexes combined

Year of discharge	SMRs for specific causes 365-days following hospital discharge with a main diagnosis of SCHIZOPHRENIA				
	Circulatory disease (ICD10: I00-I99, ICD9: 390-459)	Cancer (ICD10: C00-D48, ICD9: 140-239)	Respiratory Disease (ICD10: J00-99, ICD9: 460-519)	Accidents (ICD10: V01-X59, ICD9: E800-E929)	Suicide and undetermined intent (ICD10: X60-X84, Y10-Y34, ICD9: E950-E959, E980-E989)
1999	1.6	0.8	3.1	6.5	19.5
2000	2.0	1.0	3.5	7.5	19.6
2001	1.6	0.9	4.0	5.8	21.8
2002	1.9	1.0	4.4	4.2	17.8
2003	2.5	1.1	5.3	5.3	23.3
2004	2.2	1.1	5.6	6.8	24.7
2005	2.4	1.1	6.0	8.3	24.0
2006	2.5	1.3	4.7	6.3	20.9
p-value for trend	*0.0005*	*0.4*	*<0.0001*	*1.0*	*1.0*

Geographical variations in SMRs

In order to compare mortality across different Regional Office (RO) areas in the UK, indirectly standardised mortality ratios were calculated for each RO area by applying the national mortality rates in the general population of England to the population with SMI in each RO area in five-year age bands. This allowed the comparison of how many deaths would be expected in each RO area if the population with SMI had the same mortality rate as the general population in England, against the observed number of deaths amongst people with SMI in each area.

Table 6-21 shows that after indirectly standardising the mortality rates found in each RO area, there was a sizable though not statistically significant geographical variation in mortality for people recently discharged with a diagnosis of either condition. The region with the greatest mortality gap for people discharged with a main diagnosis of bipolar disorder in 2006 was the East of England, with an SMR of 2.5 whilst the West Midlands and the North West both had the lowest post-discharge mortality gap with an SMR of 1.3. For people discharged with a main diagnosis of schizophrenia, the East of England also had the highest post-discharge mortality gap in 2006 with an SMR of 2.9 and the North East region having the lowest risk with an SMR of 1.8.

Table 6-21 - All-cause SMRs following hospital discharge in 2006, by Government Regional Office

	All-cause SMRs following hospital discharge in 2006 (95% confidence interval)	
Regional Office	Main diagnosis of BIPOLAR DISORDER	Main diagnosis of SCHIZOPHRENIA
North East	1.7 (0.6 - 2.7)	1.8 (1.0 - 2.6)
North West	1.3 (0.6 - 1.9)	2.4 (1.7 – 3.0)
Yorkshire & Humber	2.0 (1.1 - 2.9)	1.9 (1.2 - 2.5)
East Midlands	1.7 (0.7 - 2.7)	2.0 (1.3 - 2.7)
West Midlands	1.3 (0.5 - 2.1)	2.2 (1.5 - 2.9)
East of England	2.5 (1.4 - 3.5)	2.9 (2.0 – 3.7)
London	1.8 (1.0 – 2.6)	2 (1.5 - 2.5)
South East	2.4 (1.6 - 3.3)	2.2 (1.6 - 2.7)
South West	2.3 (1.0 – 3.6)	2.0 (1.3 - 2.6)

Geographical variations of trends in SMRs

All the regions showed an increase in SMRs for people discharged with a main diagnosis of schizophrenia during the study period, with the East of England region seeing a noticeable though non-significant increase in SMR from 1.6 (95% CI: 1.1 to 2.1) in 1999 to 2.9 (95% CI: 2.0 to 3.7) in 2006. This was reflected in the non-significant Poisson tests for trend. There was no obvious pattern of geographical variation in trend for people discharged with a diagnosis of bipolar disorder.

See Table 6-22 and Table 6-23.

Table 6-22 - All-cause post-discharge SMRs for BIPOLAR DISORDER, both sexes combined, by Government Regional Office area and year

	All-cause SMRs 365-days following hospital discharge with a main diagnosis of BIPOLAR DISORDER (95% confidence interval)								
Regional Office	1999	2000	2001	2002	2003	2004	2005	2006	*p-value for trend*
North East	1.2 (0.4 - 2.1)	3.1 (1.5 - 4.7)	1.0 (0.2 - 1.7)	1.3 (0.3 - 2.3)	1.6 (0.6 - 2.6)	0.9 (0.2 – 1.6)	1.6 (0.5 - 2.8)	1.7 (0.6 - 2.7)	*1.0*
North West	1.5 (0.9 - 2.1)	1.6 (1.0 - 2.3)	1.7 (1.0 - 2.4)	1.6 (1.0 - 2.3)	1.3 (0.8 - 1.9)	1.8 (1.1 – 2.6)	1.6 (0.8 - 2.3)	1.3 (0.6 - 1.9)	*1.0*
Yorkshire & Humber	1.3 (0.6 – 2.0)	1.1 (0.5 - 1.8)	1.7 (0.9 - 2.4)	1.7 (0.9 - 2.5)	2.2 (1.3 - 3.2)	2.8 (1.8 – 3.9)	1.3 (0.6 - 2.1)	2.0 (1.1 - 2.9)	*0.8*
East Midlands	1.0 (0.3 - 1.7)	1.5 (0.7 - 2.3)	1.9 (0.9 - 2.9)	2.1 (1.1 - 3.1)	1.4 (0.6 - 2.2)	1.3 (0.5 - 2.0)	1.8 (0.8 - 2.9)	1.7 (0.7 - 2.7)	*1.0*
West Midlands	2.0 (1.1 - 2.9)	1.1 (0.5 - 1.7)	1.9 (1.0 - 2.7)	1.5 (0.7 - 2.3)	2.4 (1.4 - 3.4)	2.6 (1.5 - 3.8)	2.2 (1.1 - 3.2)	1.3 (0.5 - 2.1)	*1.0*
East of England	1.7 (0.9 - 2.5)	1.3 (0.6 - 2.1)	1.7 (0.8 - 2.5)	2.2 (1.2 - 3.1)	1.6 (0.8 - 2.4)	1.1 (0.4 - 1.8)	2.6 (1.6 - 3.7)	2.5 (1.4 - 3.5)	*0.9*
London	0.9 (0.4 - 1.5)	1.4 (0.7 - 2.1)	1.1 (0.5 - 1.7)	1.1 (0.5 - 1.7)	1.9 (1.1 - 2.6)	1.9 (1.2 - 2.6)	2.1 (1.3 - 2.9)	1.8 (1.0 – 2.6)	*0.9*
South East	1.3 (0.7 - 1.9)	1.1 (0.6 - 1.7)	1.4 (0.8 – 2.0)	2.2 (1.4 - 2.9)	1.8 (1.1 - 2.5)	1.9 (1.2 - 2.6)	1.6 (0.9 - 2.2)	2.4 (1.6 - 3.3)	*0.5*
South West	1.6 (0.7 - 2.4)	1.8 (1.0 - 2.7)	1.8 (0.9 - 2.7)	1.9 (1.0 – 2.9)	2.3 (1.2 - 3.3)	1.1 (0.4 - 1.8)	1.8 (1.0 - 2.7)	2.3 (1.0 – 3.6)	*1.0*

Table 6-23 - All-cause post-discharge SMRs for SCHIZOPHRENIA, both sexes combined, by Government Regional Office area and year

	All-cause SMRs 365-days following hospital discharge with a main diagnosis of SCHIZOPHRENIA (95% confidence interval)								
Regional Office	1999	2000	2001	2002	2003	2004	2005	2006	*p-value for trend*
North East	1.2 (0.6 - 1.7)	1.9 (1.2 - 2.6)	1.4 (0.8 - 1.9)	2.4 (1.4 - 3.4)	2.4 (1.6 - 3.3)	2.2 (1.4 – 3.0)	2.7 (1.7 - 3.7)	1.8 (1.0 - 2.6)	*0.6*
North West	1.9 (1.4 - 2.3)	1.7 (1.3 - 2.2)	1.5 (1.1 - 1.9)	1.6 (1.2 - 2.1)	2.3 (1.8 - 2.8)	2.2 (1.7 - 2.7)	2.1 (1.6 - 2.7)	2.4 (1.7 – 3.0)	*0.5*
Yorkshire & Humber	1.8 (1.3 - 2.3)	2.7 (2.0 - 3.4)	1.7 (1.2 - 2.2)	1.9 (1.3 - 2.5)	2.9 (2.2 - 3.6)	2.3 (1.6 – 3.0)	2.3 (1.6 – 3.0)	1.9 (1.2 - 2.5)	*1.0*
East Midlands	1.7 (1.1 - 2.3)	2.2 (1.6 - 2.9)	2.6 (1.8 - 3.3)	1.8 (1.2 - 2.4)	2.1 (1.3 - 2.8)	1.7 (1.0 - 2.3)	2.7 (1.8 - 3.5)	2.0 (1.3 - 2.7)	*1.0*
West Midlands	1.7 (1.2 - 2.3)	2.3 (1.6 – 3.0)	2.0 (1.4 - 2.6)	1.8 (1.2 - 2.4)	1.9 (1.3 - 2.5)	2.5 (1.8 - 3.3)	2.3 (1.5 – 3.0)	2.2 (1.5 - 2.9)	*1.0*
East of England	1.6 (1.1 - 2.1)	2.4 (1.7 – 3.0)	1.9 (1.2 - 2.6)	1.6 (1.0 - 2.1)	2.0 (1.3 - 2.7)	1.8 (1.2 - 2.5)	2.1 (1.4 - 2.8)	2.9 (2.0 - 3.7)	*0.9*
London	1.8 (1.4 - 2.3)	1.5 (1.0 - 1.9)	1.6 (1.2 – 2.0)	2.0 (1.5 - 2.5)	1.9 (1.5 - 2.4)	1.9 (1.5 - 2.4)	2.5 (1.9 - 3.0)	2.0 (1.5 - 2.5)	*0.7*
South East	1.6 (1.2 - 2.0)	1.7 (1.3 - 2.1)	1.9 (1.4 - 2.4)	2.0 (1.5 - 2.5)	2.3 (1.8 - 2.9)	2.6 (2.0 - 3.1)	2.5 (1.9 - 3.0)	2.2 (1.6 - 2.7)	*0.2*
South West	1.5 (1.0 - 1.9)	1.9 (1.4 - 2.4)	1.6 (1.1 - 2.0)	1.6 (1.1 - 2.1)	1.9 (1.3 - 2.4)	2.0 (1.4 - 2.7)	1.5 (1.0 - 2.1)	2.0 (1.3 - 2.6)	*1.0*

Absolute all-cause mortality rates

As mentioned previously, the widening mortality gap indicated by relative measure of mortality rates, in this case the SMRs, could represent an absolute rise in mortality rates in the psychiatric populations, or a fall in mortality rates in the general population in conjunction with a smaller fall in mortality rates in the psychiatric population. Accordingly, all-cause post-discharge deaths rates were calculated and plotted separately against national mortality rates over the same period, to allow the comparison of trends in the absolute difference in mortality rates between the groups.

The absolute mortality rates for people discharged from hospital with a main diagnosis bipolar disorder and schizophrenia were 15.9 per 1,000 and 14.6 per 1,000 respectively. Table 6-24 shows that the absolute mortality rate increased with increasing age.

Table 6-24 - All-cause absolute mortality rate per 1,000 population 365-days following hospital discharge in 2006

	All-cause absolute mortality rate per 1,000 population 365-days following hospital discharge in 2006 (95% confidence interval)			
Main diagnosis on discharge	All ages	< 45 yrs	45-64 yrs	65-84 yrs
BIPOLAR DISORDER	15.9 (15.6 - 16.3)	3.9 (3.8 – 4.0)	12.3 (11.9 - 12.7)	53.4 (50.7 - 56.0)
SCHIZOPHRENIA	14.6 (14.5 - 14.8)	5.7 (5.6 - 5.8)	17.4 (17.0 - 17.9)	64.4 (61.7 - 67.0)

Trend in absolute all-cause absolute mortality rates

Table 6-25 and Table 6-26, and Figure 6-2 to Figure 6-9, summarise the trend in crude and age-specific absolute mortality rates for people discharged with a diagnosis of schizophrenia or bipolar disorder during the course of this study. Whilst the absolute mortality rates in the general population declined over time, absolute rates in the populations with SMI did not. When compared with the absolute mortality rate for the general population, the mortality gap remained fairly stable for adults under 65; however for people discharged with a main diagnosis of bipolar disorder or schizophrenia between the ages of 65 and 84 years, the mortality gap widened during the study period.

Table 6-25 - All-cause post-discharge absolute mortality rate for BIPOLAR DISORDER, both sexes combined

	All-cause absolute mortality rate per 1,000 population 365-days following hospital discharge with a main diagnosis of BIPOLAR DISORDER (95% confidence interval)			
Year of discharge	All ages	< 45 yrs	45-64 yrs	65-84 yrs
1999	18.3 (17.9 - 18.8)	3.8 (3.7 - 3.9)	9.4 (9.1 - 9.7)	42.3 (40.2 - 44.4)
2000	14.2 (13.9 - 14.5)	3.7 (3.6 - 3.8)	12.4 (12 - 12.8)	44.7 (42.5 - 47)
2001	15.5 (15.2 - 15.8)	5.0 (4.9 - 5.1)	11.4 (11.0 - 11.8)	45.1 (42.83 - 47.3)
2002	17.2 (16.8 - 17.5)	4.5 (4.3 - 4.6)	13.9 (13.5 - 14.4)	54.8 (52.0 - 57.5)
2003	18.2 (17.8 - 18.6)	5.1 (5.0 - 5.3)	13.0 (12.6 - 13.4)	55.3 (52.6 - 58.0)
2004	16.3 (15.9 - 16.6)	7.4 (7.2 - 7.6)	13.1 (12.7 - 13.5)	43.4 (41.4 - 45.5)
2005	15.4 (15.1 - 15.7)	4.1 (3.9 - 4.2)	12.5 (12.0 - 12.9)	51.8 (49.3 - 54.3)
2006	15.9 (15.6 - 16.3)	3.9 (3.8 – 4.0)	12.3 (11.9 - 12.7)	53.4 (50.7 - 56.0)

Table 6-26 - All-cause post-discharge absolute mortality rate for SCHIZOPHRENIA, both sexes combined

	All-cause absolute mortality rate per 1,000 population 365-days following hospital discharge with a main diagnosis of SCHIZOPHRENIA (95% confidence interval)			
Year of discharge	All ages	< 45 yrs	45-64 yrs	65-84 yrs
1999	19.2 (18.9 - 19.4)	5.8 (5.7 - 5.9)	17.9 (17.5 - 18.4)	51.6 (49.7 - 53.5)
2000	15.7 (15.6 - 15.9)	6.2 (6.1 - 6.3)	17.8 (17.4 - 18.3)	64.1 (61.7 - 66.5)
2001	15.8 (15.6 - 16.0)	5.6 (5.5 - 5.7)	17.0 (16.6 - 17.4)	61.0 (58.6 - 63.3)
2002	15.0 (14.9 - 15.2)	5.3 (5.2 - 5.3)	16.5 (16.1 - 16.9)	57.4 (55.1 - 59.6)
2003	18.0 (17.8 - 18.2)	5.7 (5.6 - 5.8)	20.8 (20.3 - 21.3)	70.2 (67.4 - 72.9)
2004	16.6 (16.4 - 16.8)	6.1 (6.1 - 6.2)	16.8 (16.4 - 17.2)	61.5 (59.2 - 63.8)
2005	15.1 (14.9 - 15.3)	7.2 (7.1 - 7.3)	15.9 (15.5 - 16.2)	61.3 (58.9 - 63.7)
2006	14.6 (14.5 - 14.8)	5.7 (5.6 - 5.8)	17.4 (17.0 - 17.9)	64.4 (61.7 - 67.0)

Figure 6-2 - All cause post-discharge absolute mortality rate within 365-days from discharge, per 1,000 people discharged, with a main diagnosis of BIPOLAR DISORDER, all ages

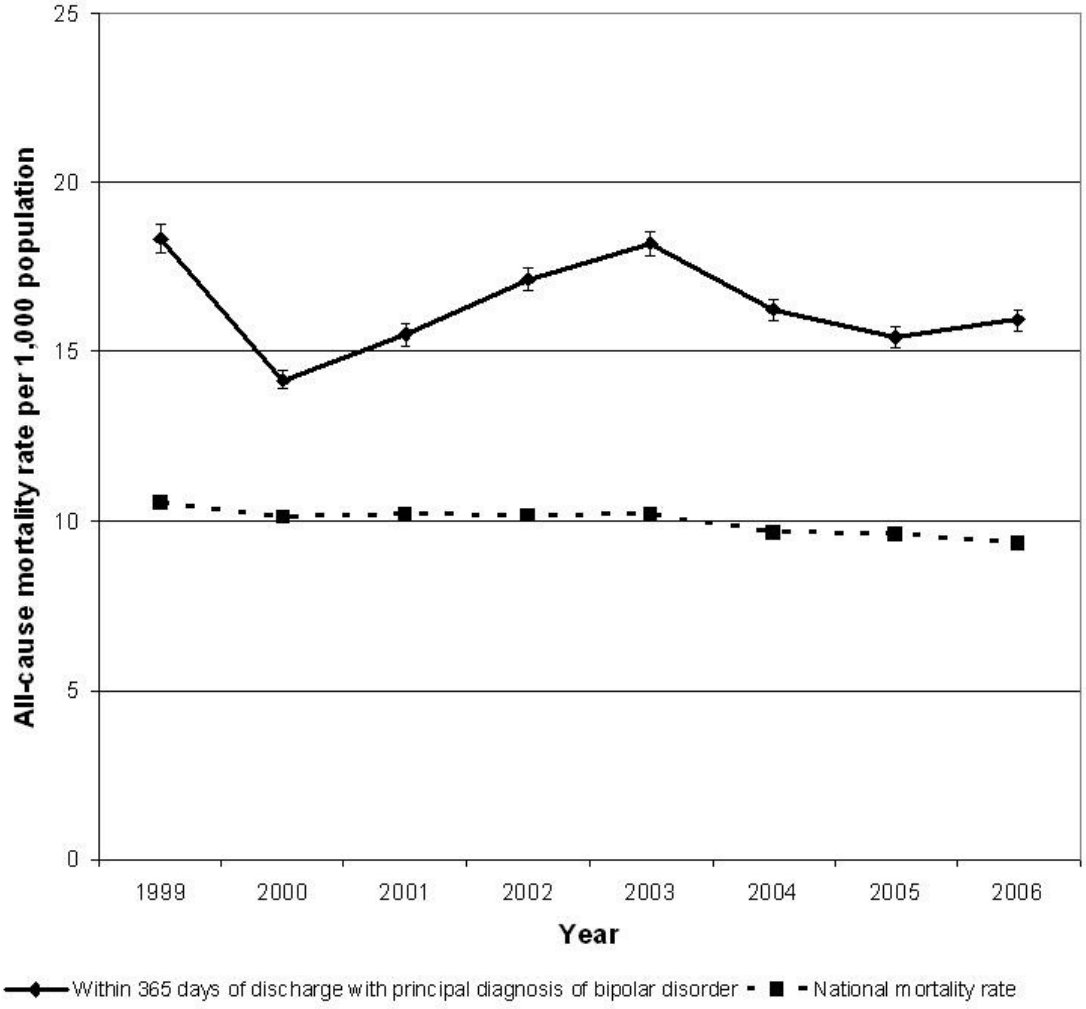


Figure 6-3 - All cause post-discharge absolute mortality rate within 365-days from discharge, per 1,000 people discharged, with a main diagnosis of SCHIZOPHRENIA, all ages

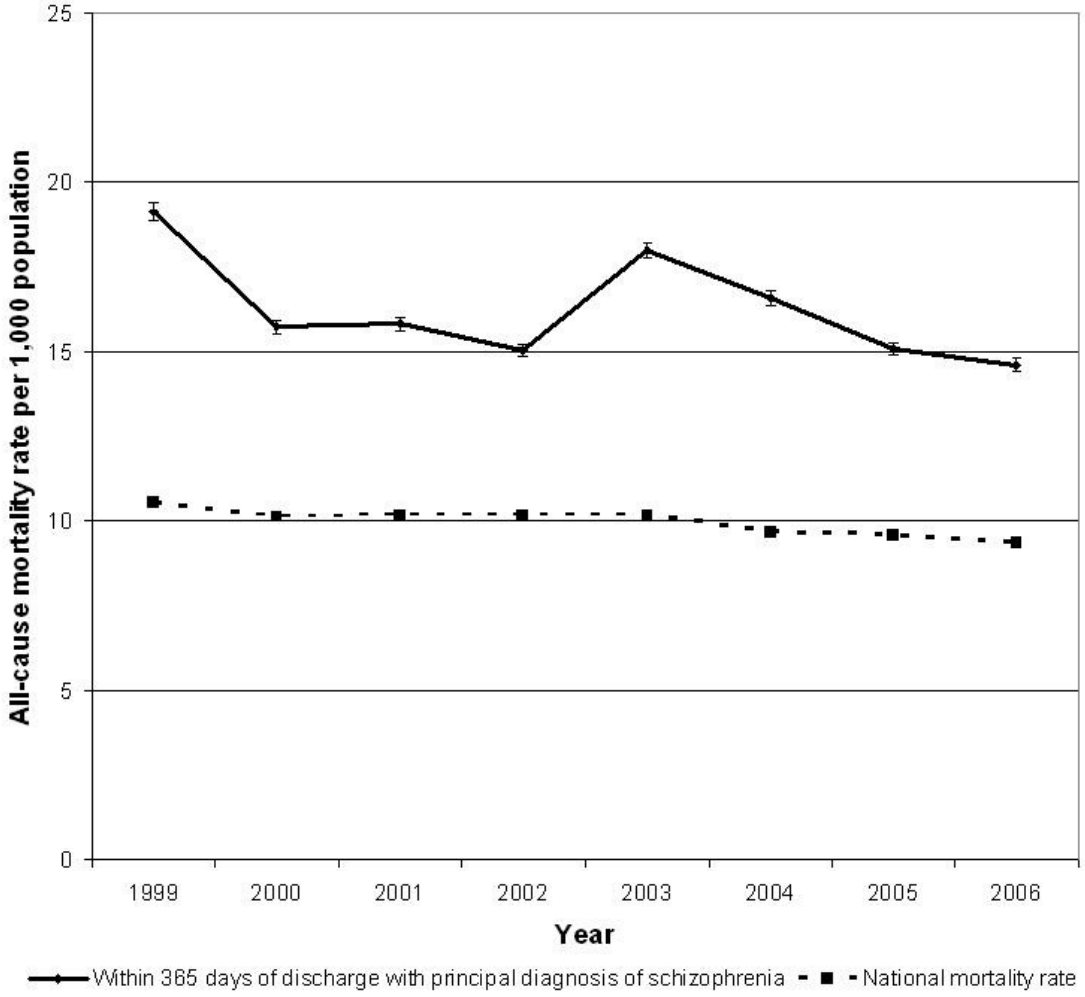


Figure 6-4 - All cause post-discharge absolute mortality rate within 365-days from discharge, per 1,000 people discharged, with a main diagnosis of BIPOLAR DISORDER, in those aged <45 years

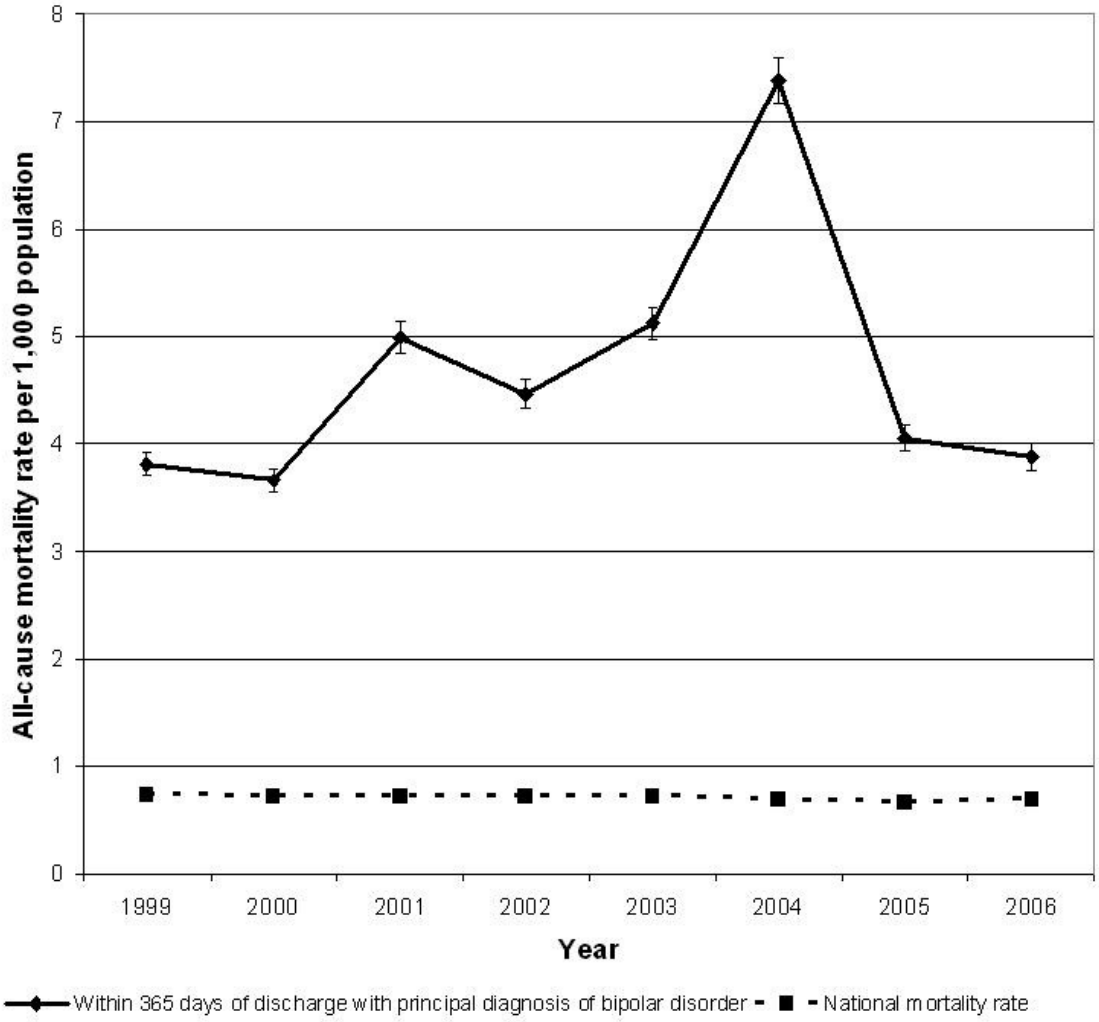


Figure 6-5 - All cause post-discharge absolute mortality rate within 365-days from discharge, per 1,000 people discharged, with a main diagnosis of SCHIZOPHRENIA, in those aged <45 years

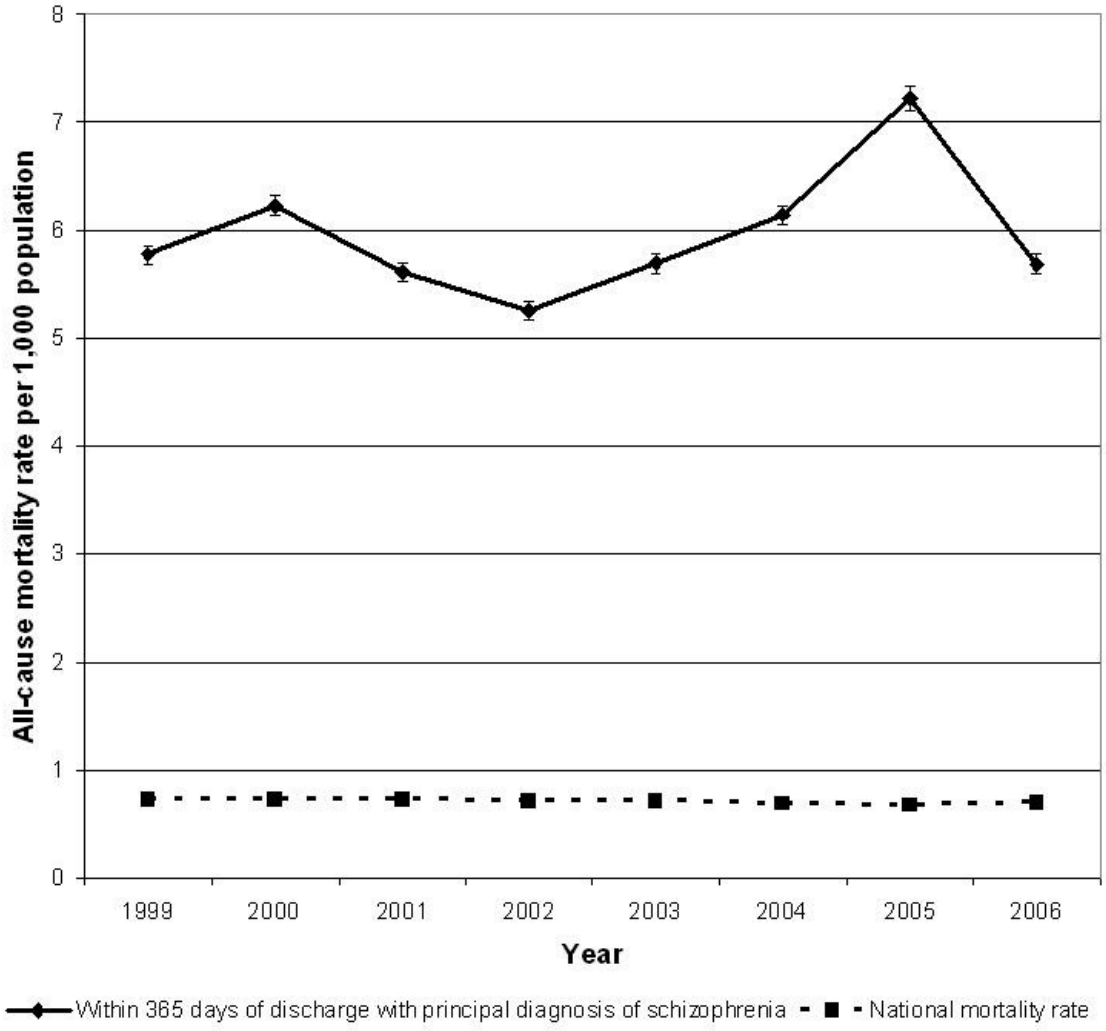


Figure 6-6 - All cause post-discharge absolute mortality rate within 365-days from discharge, per 1,000 people discharged, with a main diagnosis of BIPOLAR DISORDER, in those aged 45-64 years

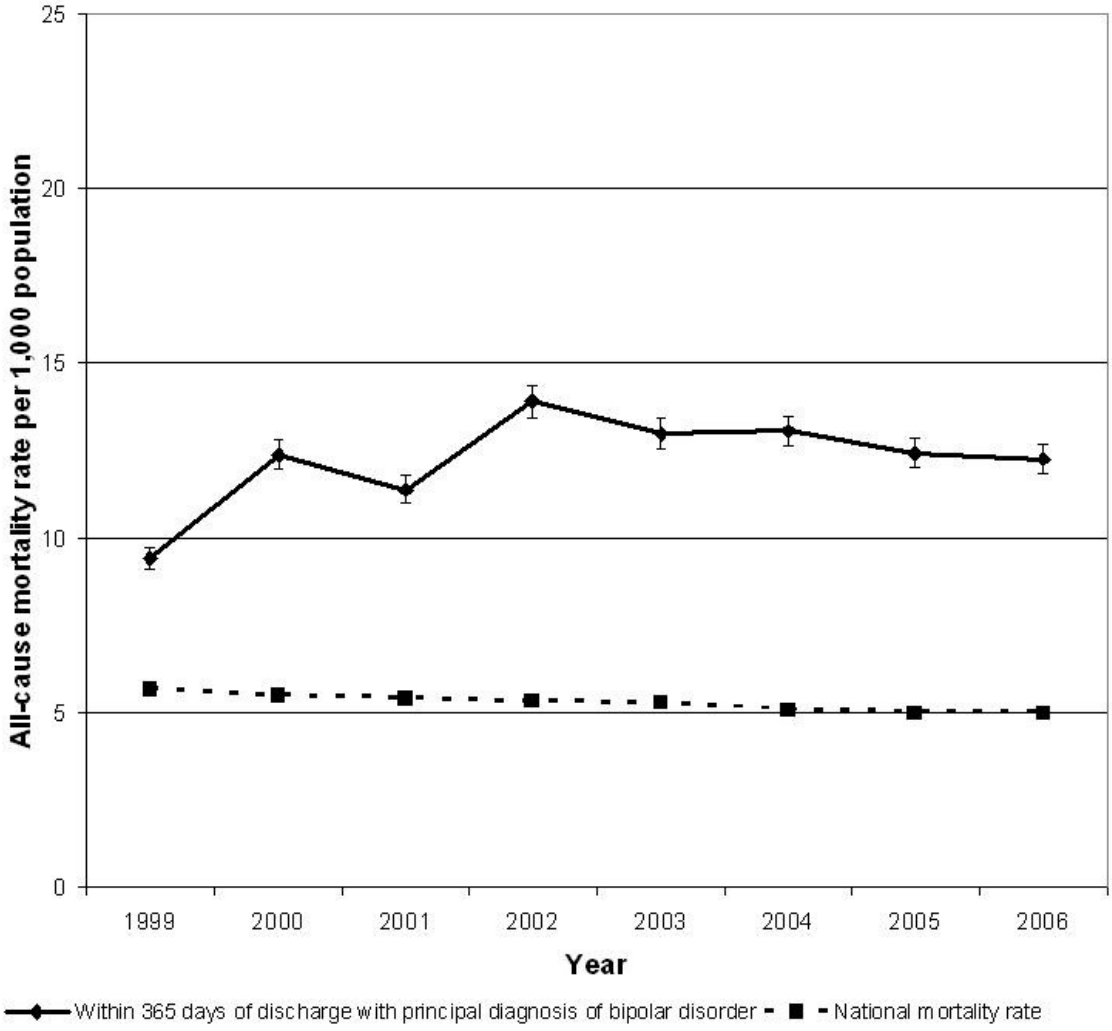


Figure 6-7 - All cause post-discharge absolute mortality rate within 365-days from discharge, per 1,000 people discharged, with a main diagnosis of SCHIZOPHRENIA, in those aged 45-64 years

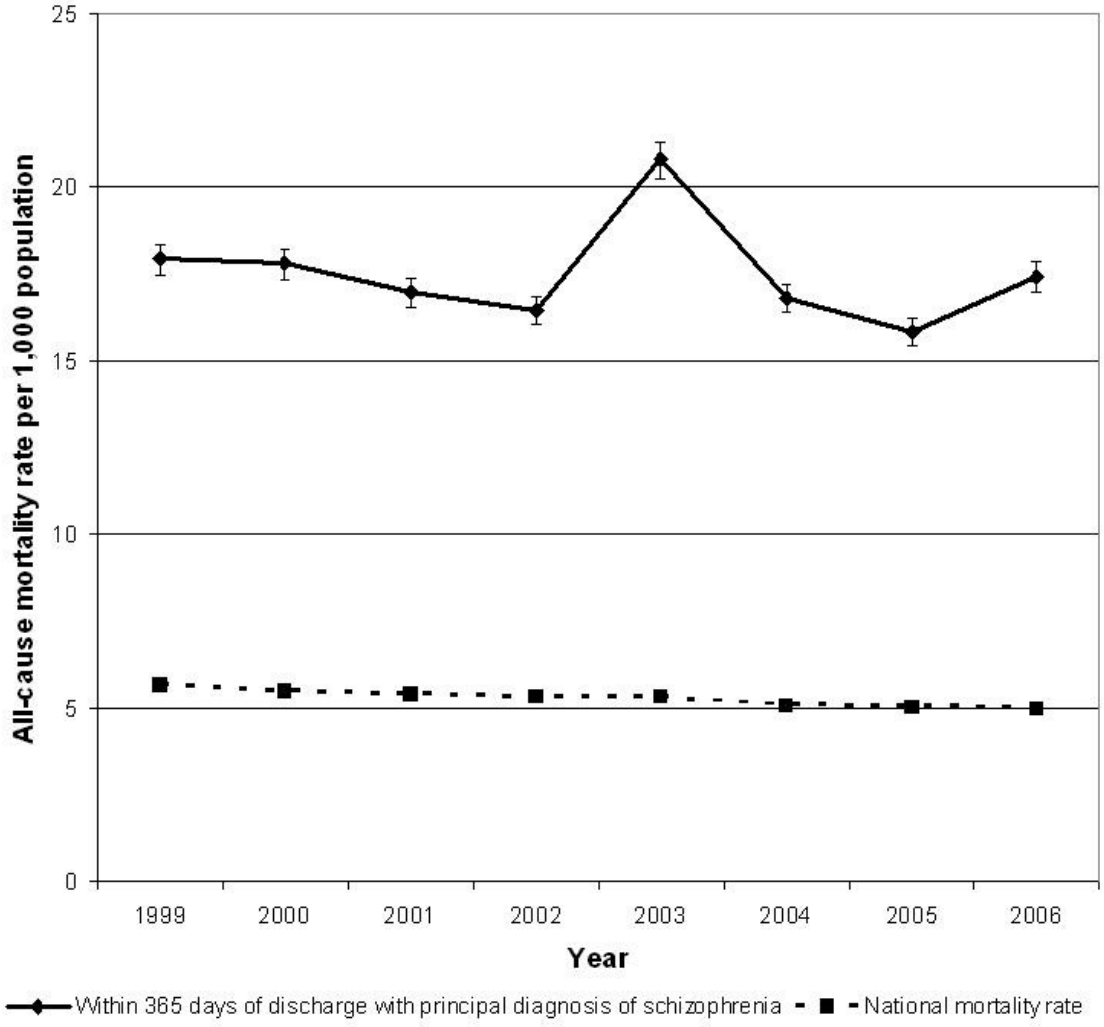


Figure 6-8 - All cause post-discharge absolute mortality rate within 365-days from discharge, per 1,000 people discharged, with a main diagnosis of BIPOLAR DISORDER, in those aged 65-84 years

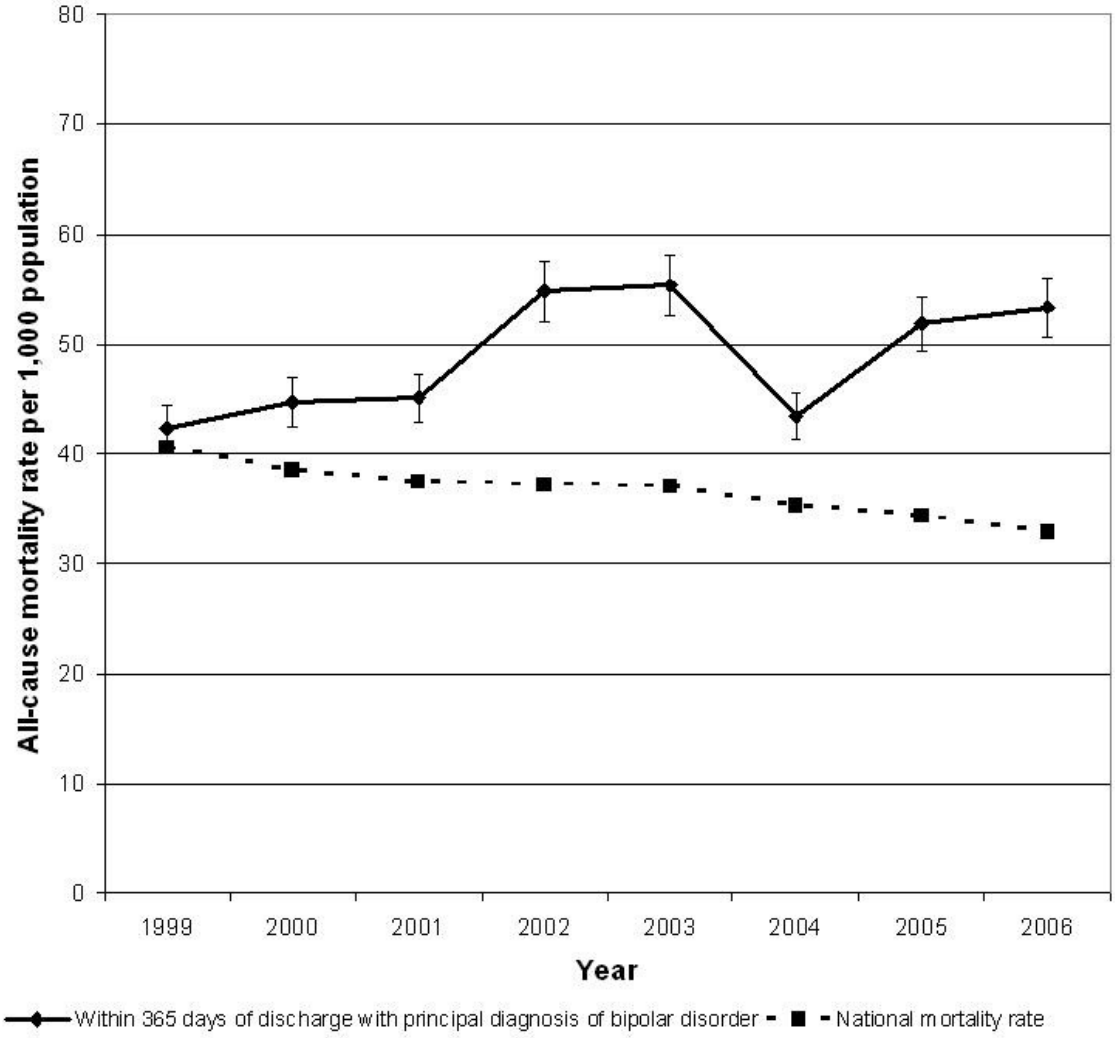
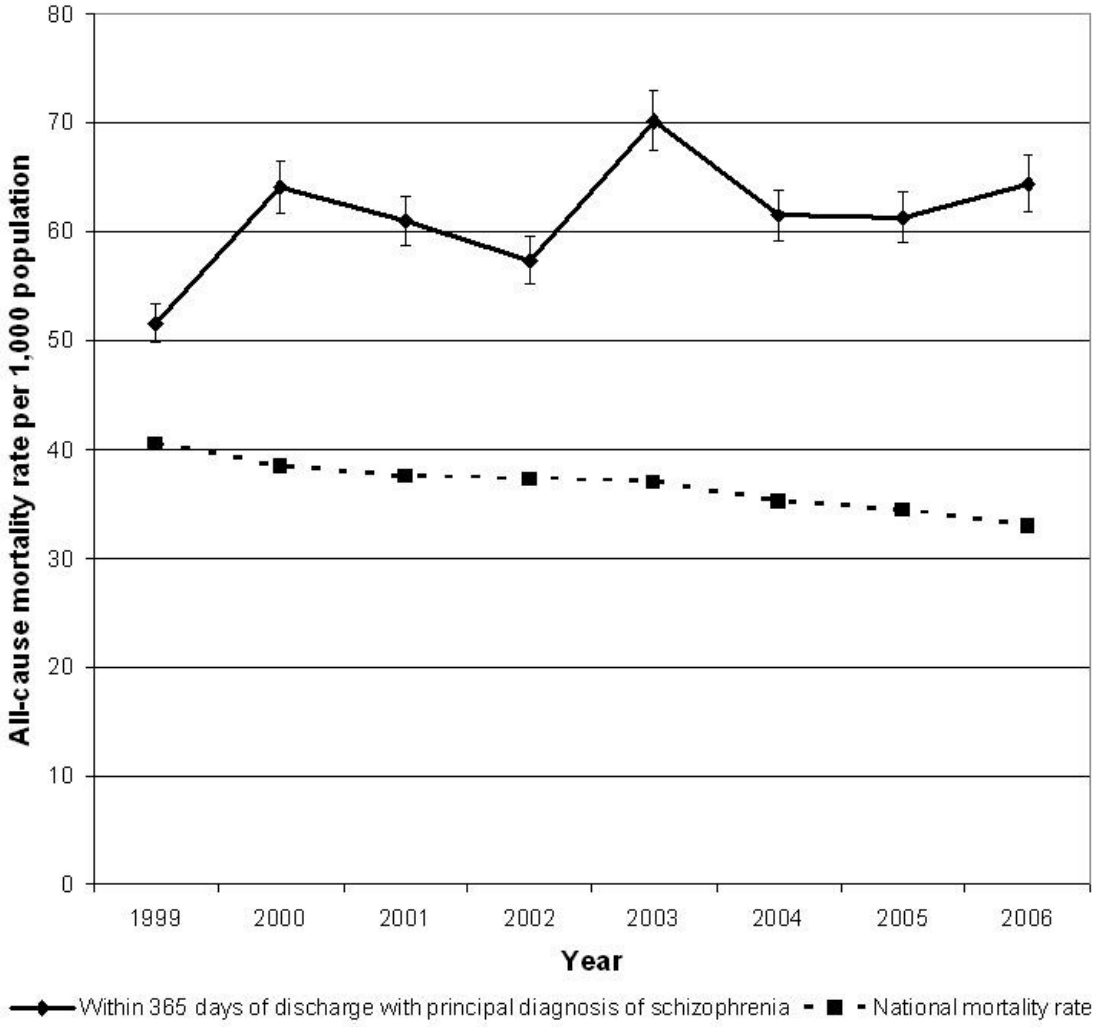


Figure 6-9 - All cause post-discharge absolute mortality rate within 365-days from discharge, per 1,000 people discharged, with a main diagnosis of SCHIZOPHRENIA, in those aged 65-84 years



Summary of findings from chapter 6

The findings from this chapter showed that

1. Inpatient care for people with bipolar disorder and schizophrenia is becoming increasingly uncommon
    - In 1999 there were 12,369 and 35,348 discharges from inpatient care for bipolar disorder and schizophrenia respectively. This decreased steadily by 3.9% and 10.9% for both conditions respectively between 1999 and 2006.
2. Deaths following discharge are rare but still important outcomes
    - The number of deaths within one year following discharge has remained stable since 1999, with approximately 1% of all discharges with a main diagnosis of bipolar disorder or schizophrenia resulting in death after one year.
    - A large component of mortality in people with a main diagnosis of bipolar disorder is due to deaths from circulatory and respiratory diseases.
3. Mortality excess for people with bipolar disorder and schizophrenia following discharge has changed over the last decade
    - After taking into account mortality in the general population over the same time period the mortality gap for both bipolar disorder and schizophrenia increased between 1999 to 2006
    - Age, sex and geographical region are also important in the determining the trend of the mortality gap
    - An examination of trends in absolute mortality rates showed that the observed trends in the mortality gap for people with these conditions was a result of a failure to benefit from the decrease in deaths experienced by the general population, and in certain groups such as people over the age of 65 years the mortality excess was a result of an absolute increase in the mortality risk in these populations

Chapter 7 – Avoidable mortality

Research question

1. What is the contribution of potentially avoidable deaths to the mortality excess experienced by people with main diagnosis of bipolar disorder and schizophrenia?
2. To what extent are causes of excess deaths potentially avoidable in people with bipolar disorder and schizophrenia and therefore what would be the impact on the mortality excess of equalising those causes in England?

Background

The mechanisms underlying mortality in people with SMI including bipolar disorder and schizophrenia are likely to be complex, however it has been suggested that a proportion of the excess mortality in these populations could be avoided either through the provision of better medical and psychiatric care, or from the provision of better preventative services for people with SMI (Wildgust and Beary 2010; Wildgust, Hodgson et al. 2010). Studies in Europe have found that people with SMI have up to three times the risk of avoidable deaths as the general population of similar age and sex (Brown, Inskip et al. 2000; Rasanen, Hakko et al. 2005; Amaddeo, Barbui et al. 2007); however, no recent studies of avoidable deaths in populations with SMI have been undertaken in the UK. Findings from the previous chapter show that adverse mortality outcome is still an important consideration in people with bipolar disorder and schizophrenia, and may be even more so as mortality has been increasing in these cohorts over the last decade, especially amongst people recently discharged from inpatient care. This lends further weight to the need to investigate the contribution of potentially avoidable deaths to the excess mortality seen (Wildgust and Beary 2010; Wildgust, Hodgson et al. 2010).

In this chapter the concept of 'avoidable mortality' will be introduced. This was originally proposed by Rutstein and colleagues in 1976, and later adopted by Walter Holland and others, to quantify the extent to which potentially avoidable causes of death contribute to the mortality excess experienced by people with bipolar disorder and schizophrenia (Rutstein, Berenberg et al. 1976; Holland, Paul et al. 1988; Holland 1993; Nolte and McKee 2004; Page, Tobias et al. 2006; Wheller, Baker et al. 2006; Wheller, Baker et al. 2007). The aim will be to adapt this concept of 'avoidable death' to answer the question of what scope is there currently to reduce the mortality gap in these populations through the implementation of public health interventions or through the provision of better medical care.

Rutstein's original paper explained the concept and definition of avoidable deaths by stating that there is 'a proportion of deaths from particular conditions, at certain ages, that should not occur in the presence of timely and effective health care or other appropriate interventions, including public health interventions' (Rutstein, Berenberg et al. 1976; Rutstein, Berenberg et al. 1980). The deaths from specific causes and the age cut-offs for which they could be applied were decided by clinical consensus. Since its publication, the concept has been applied to look at the quality of healthcare and public health services in a number of countries and specific populations, including people with severe mental illness (Holland 1993; Nolte and McKee 2003; Nolte and McKee 2004; Page, Tobias et al. 2006). Recently Wheller and colleagues updated the list of specific causes that were considered avoidable to incorporate understanding of the latest evidence on the effectiveness of medical care and public health intervention. Wheller identified the following categories of avoidable deaths (Wheller, Baker et al. 2007);

- Deaths which could be ameliorated through the efforts of health care services were termed 'amenable'.
- Deaths which could be ameliorated by broader public health interventions, for example accident prevention, were termed 'preventable'.

- Deaths which be ameliorated through the efforts of health care services or through broader public health interventions were considered ‘avoidable’ deaths (Note that some deaths classified as ‘avoidable’ were considered as both ‘amenable’ and ‘preventable’, thus the number of ‘avoidable’ deaths is not equivalent to the sum of ‘amenable’ and ‘preventable’ deaths.)

Wheller subsequently scrutinised mortality statistics in the UK and found that avoidable deaths accounted for 24% of all deaths between 1993-2005, with those that could be amenable to medical treatments accounting for 13.5% of all deaths, and those that could be prevented by public health interventions making up 17.8% (Wheller, Baker et al. 2007). However they did not examine avoidable mortality in sub-populations at high risk of death such as people with SMI.

In this chapter the definitions of avoidable deaths posited by Wheller will be used to quantify the level of ‘avoidable’ deaths in a cohort of people with a main diagnosis of bipolar disorder or schizophrenia in England in the first year following hospital discharge, often recognised as the period of highest risk for death (Goldacre, Seagroatt et al. 1993). Specifically the question of whether the mortality excess in people with bipolar disorder and schizophrenia would be reduced or eliminated if deaths in these patients from causes that should be preventable and/or amenable to treatment were reduced to their levels in the general population will be sought.

Methods

Study inclusion criteria

In order to examine the research questions posed in this chapter, all records of discharges from inpatient care in England between 1st January 2006 and 31st December 2007 with either bipolar affective disorder (ICD10 code F31), or schizophrenia (ICD10 codes F20-F29) as the main diagnosis on the discharge record were extracted from the 13 year file.

The first record in each study period with the diagnosis of interest was selected. Follow-up time was counted from the time of discharge from this first admission in the study period. Follow-up was ceased for the following reasons; 1) The patient died, 2) The patient was readmitted as an inpatient for any reason.

Thus for a patient who was admitted multiple times during the study period, only the first admission with the diagnosis of interest would be counted, other readmissions in the study period would not be counted.

Outcomes

Follow-up for 365 days after discharge, all done by record linkage within the dataset, was to 31st December 2008. The primary outcome for this chapter was mortality in people with bipolar disorder or schizophrenia compared with the general population, subdividing their excess mortality into deaths from avoidable causes and other deaths. Avoidable causes of death are selected from a list of diagnostic codes which are shown, with age ranges where relevant, in Appendix 5 (Wheller, Baker et al. 2007; 2011).

Deaths from suicide and undetermined intent (ICD10 codes - X60 to X84, Y10 to Y34) were considered avoidable if they were recorded anywhere on the death certificate, as these causes of death are rarely recorded as the underlying cause of death (Goldacre, Seagroatt et al. 1993; Hawton and Heeringen 2002; Goldacre, Duncan et al. 2006), and thus enumeration of these deaths where they are listed as the underlying cause only would substantially under-estimate the contribution of deaths from suicide and undetermined intent. Deaths from other specific causes shown in the appendix were included if they were the coded as the underlying cause of death. Deaths that were not classified as ‘avoidable’, as determined by their cause, were termed ‘unavoidable’.

Whilst the definition of avoidable deaths has been used to categorise specific causes of death previously in the general population within the UK (Wheller, Baker et al. 2007), and also for populations at high risk of death, such as people with SMI in other countries (Amaddeo, Barbui et al. 2007) as explained above, a number of points must be taken into account when considering the use of these categories for examining deaths in people with SMI. Firstly, the specific causes of death selected by a consensus of clinicians as avoidable was done so in the context of identifying diseases in the general population that would be amenable to current healthcare and public health interventions. Thus this categorisation is based on assumptions about the provision and access to care, and the ability to benefit from care. These assumptions can be tested against other studies that have compared the access, and ability to benefit from care for people with SMI and other groups, for example Lawrence and others have found that people with SMI have less access to acute cardiac care than the general population with equivalent physical ill-health (Lawrence and Kisely 2010). These results would suggest that the same list of conditions considered avoidable in the general population may not apply to people with SMI.

Secondly, quantifying avoidable deaths using routinely collected data is dependent on the accurate recording of specific causes of deaths which is known to be imprecisely recorded (Smith Sehdev and Hutchins 2001; Flaxman, Vahdatpour et al. 2011), thus this method of enumeration can only give an indication of the extent of avoidable deaths and should be verified with further studies that are able to confirm the cause of death, such as autopsy studies.

Lastly investigating specific causes of deaths in people with SMI may result in a differential measurement bias if the clinician recording the specific causes of death is not blinded to the person's diagnosis of SMI. I have discussed this in detail in chapter 9.

Analysis

Proportion and relative risk of avoidable death

In order to quantify the contribution of avoidable causes of death in people recently discharged with a main diagnosis of bipolar disorder and schizophrenia, the absolute contribution of these deaths as a proportion of total deaths is presented. The SMRs for avoidable death, or the relative rate of death from avoidable causes which takes into account the rate of avoidable deaths in the general population of the same age is also presented and allows conclusions to be made about whether the rate of avoidable deaths are more or less than expected. The standard definition of avoidable causes of death takes an upper age threshold of 74 years as the maximum age at which deaths are assumed to be avoidable (Wheller, Baker et al. 2007; 2011), thus avoidable cause SMRs are presented specifically for people under the age of 75 years.

Figure 7-1 - Calculation of hypothetical SMRs showing the all-cause SMRs that would have prevailed if excess avoidable deaths were reduced

$$\frac{\text{Observed total number of deaths}}{\text{Expected total number of deaths}} = \text{All-cause SMR}$$

A. *Calculation of the hypothetical SMR showing the effect of a reduction in excess deaths from amenable causes*

$$\frac{\text{Observed total number of deaths minus excess deaths from amenable causes}}{\text{Expected total number of deaths}} = \text{Hypothetical all-cause SMR}$$

Where: Excess deaths from amenable causes = observed – expected number of amenable deaths

B. *Calculation of the hypothetical SMR showing the effect of a reduction in excess deaths from amenable causes and suicide*

$$\frac{\text{Observed total number of deaths minus excess deaths from amenable causes and suicides}}{\text{Expected total number of deaths}} = \text{Hypothetical all-cause SMR}$$

Where: Excess deaths from amenable causes and suicide = observed – expected number of amenable deaths and suicides

C. *Calculation of the hypothetical SMR showing the effect of a reduction in excess deaths from all avoidable causes*

$$\frac{\text{Observed total number of deaths minus excess deaths from all avoidable causes}}{\text{Expected total number of deaths}} = \text{Hypothetical all-cause SMR}$$

Where: Excess deaths from avoidable causes = observed – expected number of avoidable deaths

Hypothetical SMRs

In order to analyse the possible effects on the previously observed mortality excess of a reduction in avoidable deaths in these populations, a series of hypothetical SMRs were calculated: these were the SMRs that would have prevailed if avoidable deaths were reduced to their levels in the general population. A brief explanation of the calculations undertaken is given below and in Figure 7-1. Comparable calculations have been undertaken to estimate the upper limits of human longevity (Olshansky 1992).

First, mortality from all-causes after hospital discharge was calculated as age and sex standardised mortality ratios, comparing mortality in people with schizophrenia, or bipolar disorder, with mortality in the general population of England. Standardisation was performed using the conventional indirect method, in five-year age groups, using the age- and sex-specific mortality rates of England in the same time periods as the standard. These age- and sex-specific rates were applied to the age and sex structure of each of the discharge cohorts with schizophrenia or bipolar disorder to calculate an 'expected' number of deaths. The observed number was compared with the expected number to calculate the SMRs (Hoang, Stewart et al. 2011); 95% confidence intervals for the SMRs were calculated as described elsewhere (Higham, Flowers et al. 2005).

Next, the number of excess amenable deaths was calculated by subtracting the observed number of amenable deaths from the expected number. All-cause SMRs were then re-calculated with the amenable component set to the level found in the general population. This first set of hypothetical SMRs shows what the all-cause SMR would have been if these cohorts had the same mortality rate from amenable causes as the general population, and allows one to examine the effect of a reduction in amenable deaths to the level in the general population.

As suicide and deaths from undetermined intent are an important contributor to excess deaths in people with severe mental illness, a second set of hypothetical SMRs was

calculated, in the same way, by subtracting both excess amenable deaths and excess deaths from suicide or undetermined intent. This second set of hypothetical SMRs shows what the all-cause SMR would have been if the risk of death from amenable causes and suicide in these cohorts had been the same as the general population. It allows the effect of a reduction in amenable deaths and suicide to be examined.

A final set of hypothetical SMRs were calculated by subtracting all excess avoidable causes of death. This last set of hypothetical SMRs shows what the all-cause SMR would have been if the risk of death in these cohorts from all avoidable causes had been the same as the general population. It allows one to examine the effect of a reduction in all avoidable deaths to the level in the general population.

In order to study whether the effect of reducing avoidable deaths would be more pronounced if it was targeted at all adults, adults of working age or young adults, the analysis was repeated, calculating age-truncated SMRs, for people aged under 65 years (all adults), under 45 years (working age adults) and under 25 years (younger adults),with age-sex standardisation, as above, using five year age groups within each truncated broader age group.

This analysis allows the differential effect of a reduction in avoidable deaths at different ages to be examined. The separate risks for males and females were also calculated, to examine the differential effect of a reduction in avoidable deaths for each sex.

Results

Number of discharges with a main diagnosis of bipolar disorder and schizophrenia aged under 75 years

There were 20,690 discharges with a main diagnosis of bipolar disorder (for 14,017 people) and 54,883 discharges with a main diagnosis of schizophrenia (for 37,607 people) in

England between 1st January 2006 and 31st December 2007. Table 7-1 summarises demographic characteristics of the cohorts.

Table 7-1 also shows that there were approximately 1.5 HES records per person where the main diagnosis was bipolar disorder or schizophrenia over the study period, namely two years, which is slightly higher than the ratio of 1.3 HES records per person shown in the last chapter. This is the probably due to the fact that the figures in Table 6-1 and Table 6-2 quote the ratio of HES records where the main diagnosis was bipolar disorder or schizophrenia counted over one year divided by the number of people in that year as opposed to Table 7-1 which counts the same ratio over two years.

Table 7-1 - Number of discharges and number of people aged under 75 years, discharged with a main diagnosis of BIPOLAR DISORDER or SCHIZOPHRENIA, and their demographic characteristics, between 2006-07, in England

	Main diagnosis on discharge	
	BIPOLAR DISORDER	SCHIZOPHRENIA
Number of discharges between 1st Jan 2006- 31st Dec 2007	20,690	54,883
Number of people discharged between 1st Jan 2006- 31st Dec 2007	14,017	37,607
% male	41	62
Deaths from all causes within 365 days of discharge	169	480
Number of deaths that are amenable (% of all deaths)	51 (30.2%)	145 (30.2%)
Number of deaths that are preventable** (% of all deaths)	83 (49.1%)	243 (50.6%)
Number of deaths that are avoidable** (% of all deaths)	100 (59.2%)	289 (60.2%)

*Consultation on definitions of avoidable mortality (2011)

** Deaths from suicide and undetermined intent (ICD10 codes - X60 to X84, Y10 to Y34) were included in this group

*** Note that many conditions classified as ‘avoidable’ are classified as both ‘amenable’ and ‘preventable’, thus the first two categories do not sum to the last

All-cause mortality rate and proportion of deaths from avoidable causes in people with bipolar disorder and schizophrenia

Within 365 days of discharge, there were 169 deaths for people under 75 years who had recently been discharged with a main diagnosis of bipolar disorder and 480 deaths amongst people recently discharged with a main diagnosis of schizophrenia (see Table 7-1). Avoidable deaths comprised 59·2% of all deaths for people recently discharged with a main diagnosis of bipolar disorder. Amenable deaths accounted for 30·2%, whilst preventable deaths accounted for 49·1% of all deaths (many causes on the list are regarded as both amenable and preventable). The SMR for avoidable deaths under 75 years was 3.8 (95% CI: 3.2–4.4).

For people under 75 years recently discharged with a main diagnosis of schizophrenia, avoidable deaths comprised 60·2% of all deaths. Deaths potentially amenable to medical care accounted for 30·2% of deaths, whilst deaths from conditions that are potentially preventable through public health interventions accounted for 50·6% of all deaths (see Table 7-1). The SMR for avoidable deaths under 75 in people with schizophrenia was 5.4 (95% CI: 4.9–5.9), which is similar to previously published results on avoidable mortality in England and other countries in Europe (Brown, Inskip et al. 2000; Rasanen, Hakko et al. 2005; Amaddeo, Barbui et al. 2007). 'Unavoidable' deaths, namely those deaths that remained after discounting 'avoidable' deaths, were distributed rather generally across major disease groups, without heavy concentration in any disease category (see Table 7-2).

Table 7-2 - Underlying causes of death within 365 days after discharge in people with a principal diagnosis of BIPOLAR DISORDER or SCHIZOPHRENIA, and the percentage of deaths in each disease chapter that were from unavoidable causes

Underlying cause of death 365 days after discharge (ICD10 chapter headings and code ranges)	Total number of deaths	Number of deaths that were unavoidable (% of all deaths)	Total number of deaths	Number of deaths that were unavoidable (% of all deaths)
	BIPOLAR DISORDER		SCHIZOPHRENIA	
Deaths from all-causes	169	69 (40.8%)	480	191 (39.8%)
Deaths from certain infectious and parasitic diseases (ICD10 codes - A00-B99)	7	1 (14·3%)	14	3 (21·4%)
Neoplasms (ICD10 codes - C00-D48)	21	13 (61·9%)	48	23 (47·9%)
Diseases of the circulatory system (ICD10 codes – I00-I99)	41	13 (31·7%)	125	49 (39·2%)
Diseases of the respiratory system (ICD10 codes – J00-J99)	25	0 (0%)	86	25 (29·1%)
Diseases of the digestive system (ICD10 codes - K00-K93)	8	7 (87·5%)	17	15 (88·2%)

Standardised Mortality Ratios

The all-cause SMRs for people discharged between 1st Jan 2006 and 31st Dec 2007 with a main diagnosis of bipolar disorder or schizophrenia under the age of 75 were, respectively, 2·6 (95% CI: 2·2–3·0) and 4·23 (95% CI: 3·9-4·6).

Table 7-3, Figure 7-2 and Figure 7-3 show that equalising amenable deaths for people with a main diagnosis of bipolar disorder resulted in the all-cause SMRs falling from 2·6 to 2·2 (95% CI: 1·8– 2·6). For people with a main diagnosis of schizophrenia the all-cause SMRs fell from 4·2 to 3·3 (95% CI: 3·0-3·7) in this way.

Additionally equalising mortality from suicide gave a further reduction in the all-cause SMRs to 1·7 (95% CI: 1·4-2·0) for people with a main diagnosis of bipolar disorder and to 2·4 (95% CI: 2·2-2·7) for people with a main diagnosis of schizophrenia.

Finally, equalising amenable deaths, suicides and all other preventable deaths did not eliminate the mortality gap, the all-cause SMRs remaining at 1·7 (95% CI: 1·4-2.0) for people with a main diagnosis of bipolar disorder and 2·4 (95% CI: 2·1-2·7) for people with a main diagnosis of schizophrenia.

Table 7-3 - Hypothetical SMRs for people aged under 75 years and discharged with a main diagnosis of BIPOLAR DISORDER or SCHIZOPHRENIA, applying death rates from amenable causes, suicide and preventable causes at the levels in the general population

BOTH SEXES, aged under 75 years

Category	SMR within 365 days after discharge (95% CI)	
	Main diagnosis on discharge of BIPOLAR DISORDER	Main diagnosis on discharge of SCHIZOPHRENIA
All-causes	2·6 (2·2 - 3·0)	4·2 (3·9 – 4·6)
All-causes minus excess amenable deaths*	2·2 (1·8 – 2·6)	3·3 (3 – 3·7)
All-causes minus excess amenable deaths* and suicides or deaths from undetermined intent	1·7 (1·4 – 2.0)	2·4 (2·2 – 2·7)
All-causes minus excess amenable deaths*, suicides or deaths from undetermined intent, and preventable deaths*	1·7 (1·4 – 2.0)	2·4 (2·1 – 2·7)

*(Wheller, Baker et al. 2007)

Figure 7-2 - Hypothetical SMRs for people aged under 75 years and discharged with a main diagnosis of BIPOLAR DISORDER, applying death rates from amenable causes, suicide and preventable causes at the levels in the general population

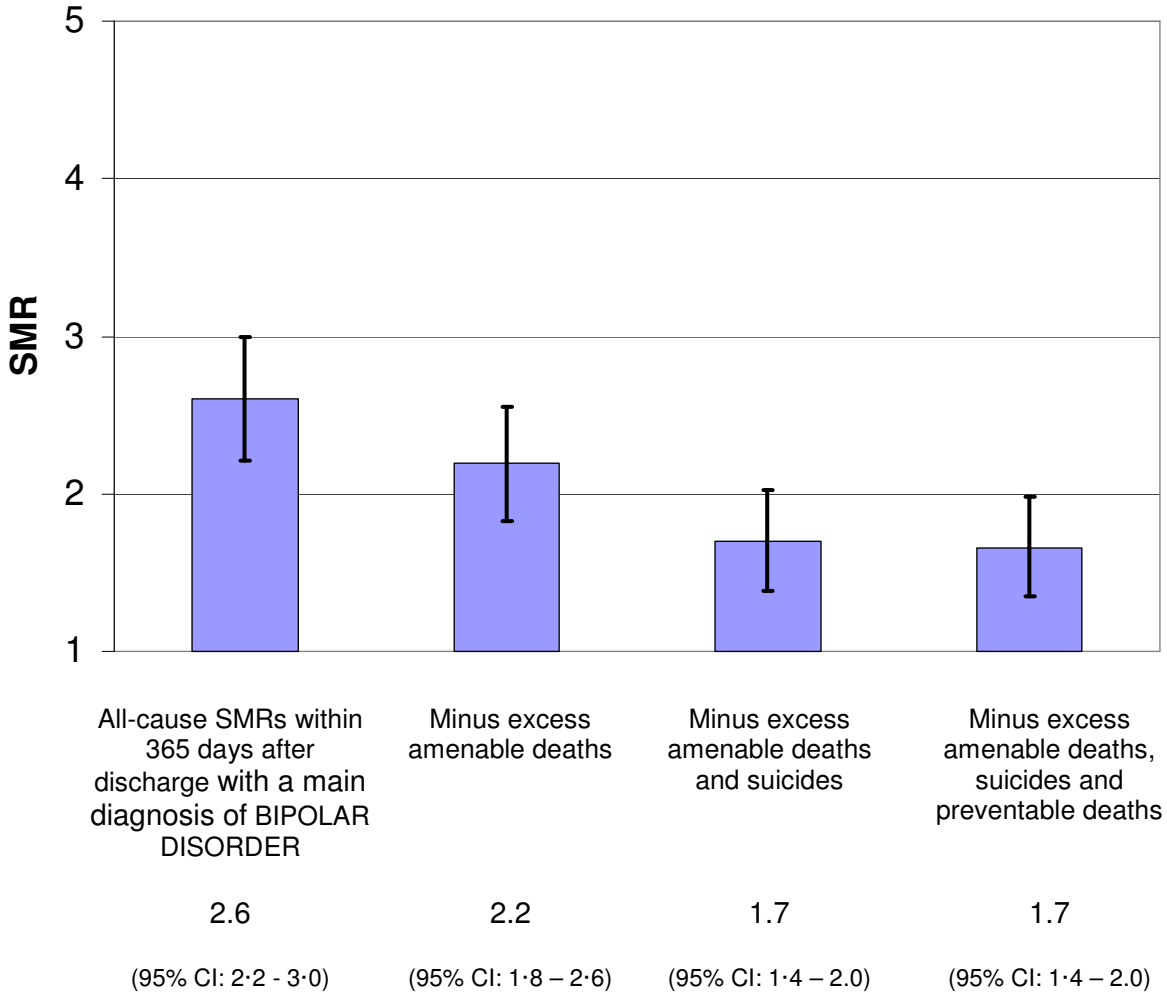
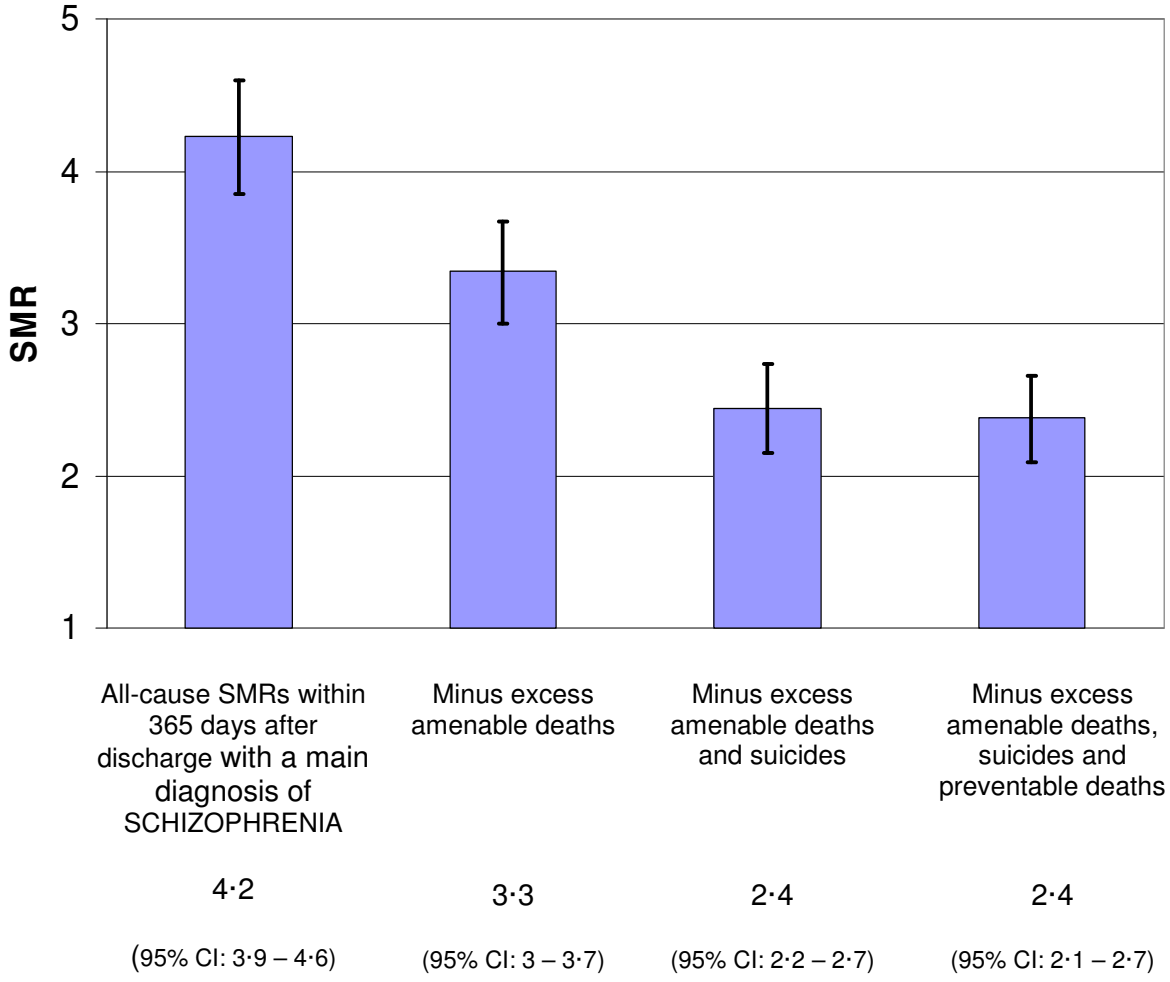


Figure 7-3 - Hypothetical SMRs for people aged under 75 years and discharged with a main diagnosis of SCHIZOPHRENIA, applying death rates from amenable causes, suicide and preventable causes at the levels in the general population



As shown previously and also in Table 7-4 shows differences between men and women in the mortality gap with the general population, especially for people with a main diagnosis of schizophrenia. Sex-specific SMRs were higher in men than women especially with a main diagnosis of schizophrenia; reducing deaths from avoidable causes had a marginally greater impact on men than women. For example the SMR for men with a main diagnosis of schizophrenia decreased from 4·6 (95% CI: 4.1 – 5.1) to 2·5 (95% CI: 2·1 – 2·9) if all avoidable causes of death were reduced, compared with a reduction from 3.7 (95% CI: 3.1 – 4·2) in women to 2·2 (95% CI: 1.7 – 2·6). There was no difference between men and women when reducing avoidable causes in people with a main diagnosis of bipolar disorder.

Table 7-4 - Hypothetical SMRs for people aged under 75 years discharged with a main diagnosis of BIPOLAR DISORDER or SCHIZOPHRENIA, applying death rates from amenable causes, suicide and preventable causes at the levels in the general population, by sex

A. MALES, aged under 75 years

Category	SMR within 365 days after discharge (95% CI)	
	Main diagnosis on discharge of BIPOLAR DISORDER	Main diagnosis on discharge of SCHIZOPHRENIA
All-causes	2·7 (2·1 - 3·3)	4·6 (4.1 – 5.1)
All-causes minus excess amenable deaths*	2·3 (1·8 – 2·9)	3·5 (3·1 – 4)
All-causes minus excess amenable deaths* and suicides or deaths from undetermined intent	1·8 (1·3 – 2·3)	2·5 (2·1 – 2·9)
All-causes minus excess amenable deaths*, suicides or deaths from undetermined intent, and preventable deaths*	1·7 (1·2 – 2.1)	2·5 (2·1 – 2·9)

*(Wheller, Baker et al. 2007)

B. FEMALES, aged under 75 years

Category	SMR within 365 days after discharge (95% CI) Main diagnosis on discharge of BIPOLAR DISORDER	Main diagnosis on discharge of SCHIZOPHRENIA
All-causes	2·9 (2·3 - 3·4)	3.7 (3.1 – 4·2)
All-causes minus excess amenable deaths*	2·3 (1·8 – 2·8)	3.0 (2.5 – 3·5)
All-causes minus excess amenable deaths* and suicides or deaths from undetermined intent	1·8 (1·3 – 2·3)	2·4 (1.9 – 2·8)
All-causes minus excess amenable deaths*, suicides or deaths from undetermined intent, and preventable deaths*	1·8 (1·3 – 2.3)	2·2 (1.7 – 2·6)

*(Wheller, Baker et al. 2007)

Further age-truncated analysis suggests that reducing avoidable deaths in people <45 years would have the greatest age-specific effect on reducing excess mortality. Table 7-5 shows that people with a main diagnosis of bipolar disorder <45 years would experience a reduction of SMR from 3.7 (95% CI: 2·3–5.1) to 1·6 (95% CI: 0.7–2.5), whilst people with a main diagnosis of schizophrenia <45 years would experience a reduction of SMR from 7·1 (95% CI: 6.0–8.2) to 3·3 (95% CI: 2·6 – 4.1) if all avoidable causes of death were reduced to the same level as the general population.

Table 7-5 - Hypothetical SMRs for people aged under 65, under 45 and under 25 discharged with a main diagnosis of BIPOLAR DISORDER or SCHIZOPHRENIA, applying death rates from amenable causes, suicide and preventable causes at the levels in the general population

A. Both sexes, aged UNDER 65 YEARS

Category	SMR within 365 days after discharge (95% CI)	
	Main diagnosis on discharge of BIPOLAR DISORDER	Main diagnosis on discharge of SCHIZOPHRENIA
All-causes	3.0 (2·4 - 3·5)	5.2 (4.7 – 5.8)
All-causes minus excess amenable deaths*	2·7 (2.2 – 3.3)	4.3 (3.8 – 4.8)
All-causes minus excess amenable deaths* and suicides or deaths from undetermined intent	1·9 (1·4 – 2·3)	2·9 (2·5 – 3.3)
All-causes minus excess amenable deaths*, suicides or deaths from undetermined intent, and preventable deaths*	1·8 (1·4 – 2.3)	2·8 (2·4 – 3.2)

*(Wheller, Baker et al. 2007)

B. Both sexes, aged UNDER 45 YEARS

Category	SMR within 365 days after discharge (95% CI)	
	Main diagnosis on discharge of BIPOLAR DISORDER	Main diagnosis on discharge of SCHIZOPHRENIA
All-causes	3.7 (2·3 – 5.1)	7·1 (6.0 – 8.2)
All-causes minus excess amenable deaths*	3.6 (2.2 – 5.0)	6.7 (5.6 – 7.8)
All-causes minus excess amenable deaths* and suicides or deaths from undetermined intent	1·7 (0.8 – 2·7)	3.5 (2·7 – 4.3)
All-causes minus excess amenable deaths*, suicides or deaths from undetermined intent, and preventable deaths*	1·6 (0.7 – 2.5)	3·3 (2·6 – 4.1)

*(Wheller, Baker et al. 2007)

C. Both sexes, aged UNDER 25 YEARS

Category	SMR within 365 days after discharge (95% CI) Main diagnosis on discharge of BIPOLAR DISORDER	SMR within 365 days after discharge (95% CI) Main diagnosis on discharge of SCHIZOPHRENIA
All-causes	1.9 (0 - 4·0)	5.3 (3·2 – 7.4)
All-causes minus excess amenable deaths*	1.9 (0 - 4·0)	4.9 (2.9 – 6.9)
All-causes minus excess amenable deaths* and suicides or deaths from undetermined intent	1·4 (0 – 3.3)	2·5 (1.0 – 4.0)
All-causes minus excess amenable deaths*, suicides or deaths from undetermined intent, and preventable deaths*	1·3 (0 – 3.1)	2·2 (0.8 – 3.5)

*(Wheller, Baker et al. 2007)

Summary of findings from chapter 7

The findings from this chapter showed that

1. Avoidable deaths are a substantial contributor to overall mortality in people discharged with a main diagnosis of bipolar disorder and schizophrenia
    - Avoidable causes accounted for 59·2% of all deaths in people recently discharged with a main diagnosis of bipolar disorder, and 60·2% of all deaths in people with a main diagnosis of schizophrenia
2. Potentially avoidable causes of death are an important contributor to the mortality excess seen in these conditions
    - The SMR for avoidable deaths in people under 75 years recently discharged with a main diagnosis of bipolar disorder was 3.8 (95% CI: 3.2–4.4), and for people with a main diagnosis of schizophrenia it was 5.4 (95% CI: 4.9–5.9)
3. Unavoidable causes of death were distributed across a broad range of disease groups
4. Current approaches including health care interventions and public health policies to reduce mortality would be expected to reduce the overall mortality excess in SMI by about 50% in people under the age of 75 years, but not entirely eliminate this well known disparity. In fact reducing avoidable deaths in people with SMI <45 years would have the greatest age-specific effect on reducing excess mortality.

Chapter 8 – Mortality in people with comorbid bipolar disorder and schizophrenia

Research question

Does comorbid illness with bipolar disorder and schizophrenia in people with another main diagnosis, namely cardiovascular disease or diabetes, result in excess mortality?

Background

In the previous chapters an excess risk of mortality was found, including death from avoidable causes, in people with a recent main diagnosis of bipolar disorder and schizophrenia on discharge, and the mortality gap was found to have been increasing over the last decade. However, the results may have underestimated the true extent of the mortality gap as a result of these conditions as, up to now in this thesis, only the mortality gap for people who have been discharged from hospital with a main diagnosis of bipolar disorder or schizophrenia has been considered. Previous research found that mortality risk extends to people who are affected primarily by a physical illness, and have a severe mental illness as a comorbid condition. Most evidence relates to adverse outcomes in people who present with cardiovascular disease or diabetes, and have comorbid SMI. (Lawrence, Holman et al. 2000; Lesperance, Frasure-Smith et al. 2000; Jaffe, Krumholz et al. 2006; Lawrence and Kisely 2010; Lawrence, Kisely et al. 2010). For example Osborn and colleagues used information from the UK General Practice Research Database (GPRD) to show that there is a high risk of cardiovascular and stroke deaths in people with SMI not explained by the presence of common risk factors including anti-psychotic drug use, smoking or social deprivation (Osborn, Levy et al. 2007). There may be a number of reasons for these findings including;

- people with SMI may present with more severe physical illness disease as a result of late presentation (Lawrence, Holman et al. 2000; Kessler, Chiu et al. 2005; Callahan and Khizar 2010)
- people with SMI may have difficulty accessing physical healthcare services and difficulty with compliance with ongoing medical care (Ussher, Stanbury et al. 2007; Kisely, Campbell et al. 2009; Lawrence and Kisely 2010; Mitchell and Lord 2010)
- ongoing treatments for mental illness, such as the adverse effects of anti-psychotics may complicate the management of physical illness (Barak, Baruch et al. 2007; Laursen, Munk-Olsen et al. 2009; Blasco-Fontecilla, Baca-Garcia et al. 2010)

Other studies have found the opposite result with people with comorbid SMI having lower mortality, especially in the short-term (Abrams, Vaughan-Sarrazin et al. 2008; Abrams, Vaughan-Sarrazin et al. 2009; Abrams, Vaughan-Sarrazin et al. 2010). A number of explanations have been put forward for this including;

- medical record coding may be more likely to include a psychiatric comorbidity in patients with less complicated hospital courses of illness
- providers may be more vigilant or be more likely to intervene in patients with physical illness and psychiatric comorbidities
- people with physical illness and psychiatric comorbidities may experience lower utilization of invasive diagnostic or potentially harmful therapeutic procedures

Given the previous evidence of an increasing mortality gap for people with a main diagnosis of bipolar disorder and schizophrenia in England, and the evidence from other countries of the importance of comorbid SMI on mortality, but the lack of previous research in the UK, I will aim to explore the question of whether having a co-existing diagnosis of bipolar disorder or schizophrenia in people admitted with a main diagnosis of cardiovascular disease or diabetes puts people at greater risk of death.

Method

Study inclusion criteria

In order to examine the research questions posed in this chapter, all records of inpatient care in England between 1st January 2007 and 31st December 2007 with a main diagnosis of either cardiovascular disease (ICD10 codes I00–I99), or diabetes (ICD10 codes E10-E14), were extracted.

Within these inpatient cohorts, people with comorbid bipolar disorder (ICD10 code F31) or schizophrenia (ICD10 codes F20–F29) were identified by searching for the diagnosis anywhere else on the same hospital record. However data from the NHS Information Centre (NHS IC) suggests that the accuracy of secondary diagnostic coding, i.e. codes other than the main diagnosis is approximately 75% for a variety of diagnosis (Spencer 2011). Additionally this technique to identify comorbid SMI has been criticised by Abrams and colleagues who suggest that it may selectively miss people with more severe comorbid mental disorders, and under-estimate the association between psychiatric comorbidity and mortality (Abrams, Vaughan-Sarrazin et al. 2008), thus the hospital records were searched to identify people who may also have been admitted for inpatient care with a main diagnosis of bipolar disorder or schizophrenia within the past year. This served as a second method of defining the study group.

Again the counting method included the first record in each study period with the diagnoses of interest. Follow-up time was counted from the time of discharge from this first admission in the study period. Follow-up was ceased for the following reasons; 1) The patient died, 2) The patient was readmitted as an inpatient for any reason.

Thus for a patient who was admitted multiple times during the study period, then only the first admission with the diagnoses of interest would be counted, other readmissions in the study period would not be counted.

Outcomes recorded and analysis plan

The primary outcome for this chapter was mortality from all-causes within 365 days after admission. First, a description of patient characteristics and unadjusted post-admission mortality rates is presented in people with and without a comorbid diagnosis of bipolar disorder or schizophrenia as defined above. Second, the mortality risk was compared using survival analysis to calculate the hazard ratio controlling for age and sex differences between the two groups. Survival curves were plotted for people with and without comorbid SMI to facilitate comparison of the mortality risk in the two groups.

Results

Characteristics of people admitted with a main diagnosis of cardiovascular disease in 2007

There were 717,556 admissions for 542,848 people with a main diagnosis of cardiovascular disease between 1st January and 31st December 2007 in England. Their demographic profile is shown in Table 8-1.

Table 8-1 shows that there were approximately 1.3 HES records per person where the main diagnosis was cardiovascular disease over one year, which is similar to than the ratio of 1.3 HES records per person shown in chapter 6 for SMI over the same period.

Table 8-1 - Characteristics of people admitted with a main diagnosis of cardiovascular disease (CVD) in 2007

	All admitted with a main diagnosis of CVD (ICD10 codes I00 to I99)
Number of admissions	717,556
Number of people	542,848
Number of males discharge (%)	300,160 (55.3%)
Average age at discharge (males/ females)	74.6/ 79
Average length of stay (males/ females)	8.1/ 10
Number of deaths within 365 days of admission	54,687
Unadjusted death rates per 1,000 admissions (95% CI)	100.7 (99.9 – 101.6)

Characteristics of people admitted with a main diagnosis of cardiovascular disease and comorbid SMI

Of people admitted with a main diagnosis of cardiovascular disease, 0.07-0.1% had comorbid bipolar disorder according to whether the diagnosis of bipolar disorder was noted as a secondary diagnosis on the same hospital record or if the diagnosis of bipolar disorder was recorded as the main diagnosis within the past year (see Table 8-2 and Table 8-3). Comorbid schizophrenia was present in 0.2 - 0.3% of the cohort, using the same inclusion criteria (see Table 8-4 and Table 8-5). Although all people with a main diagnosis of schizophrenia have been included in these proportions, the figures of hospital comorbidity are slightly less than the annual prevalence of schizophrenia of 0.5% recorded in a US sample (Wu, Shi et al. 2006) but similar to prevalence recorded in non-Maori populations in New Zealand (Kake, Arnold et al. 2008).

People with comorbid bipolar disorder or schizophrenia were slightly younger than those without comorbid SMI, and people with comorbid bipolar disorder were more likely to be female. The average length of stay for people with comorbid SMI depended on how the comorbid sample was selected. People who had a diagnosis of schizophrenia or bipolar disorder as a secondary diagnosis on their hospital record had longer average length of stays than people with no comorbid SMI (see Table 8-2 to Table 8-5).

Table 8-2 - Characteristics of people admitted with a main diagnosis of CVD in 2007 and comorbid bipolar disorder defined as secondary diagnosis of BIPOLAR DISORDER on the same hospital record

	Main diagnosis of CVD and comorbid bipolar disorder	No comorbid bipolar disorder
Number of admissions	980	716,576
Number of people	737	542,111
Number of males (%)	332 (45%)	299,787 (55.3%)
Average age at discharge (males/ females)	62.2/ 65.4	74.6/ 79
Average length of stay (males/ females)	12.2/ 11.6	7.9/ 9.7
Number of deaths within 365 days of admission	47	54,640
Unadjusted death rates per 1,000 admissions (95% CI)	63.7 (47.4 – 84.1)	100.8 (100.0 – 101.6)

Table 8-3 - Characteristics of people admitted with a main diagnosis of CVD in 2007 and comorbid bipolar disorder defined by recent discharge with main diagnosis of BIPOLAR DISORDER in the past year

	Main diagnosis of CVD and comorbid bipolar disorder	No comorbid bipolar disorder
Number of admissions	566	716,990
Number of people	428	542,420
Number of males (%)	181 (42.3%)	299,958 (55.3%)
Average age at discharge (males/ females)	61.5/ 65.3	74.6/ 79
Average length of stay (males/ females)	6.8/ 8.6	7.9/ 9.7
Number of deaths within 365 days of admission	32	54,655
Unadjusted death rates per 1,000 admissions (95% CI)	74.8 (52.0 – 104.3)	100.8 (99.9 – 101.6)

Table 8-4 - Characteristics of people admitted with a main diagnosis of CVD in 2007 and comorbid schizophrenia defined as secondary diagnosis of SCHIZOPHRENIA on the same hospital record

	Main diagnosis of CVD and comorbid schizophrenia	No comorbid schizophrenia
Number of admissions	2145	715,411
Number of people	1603	541,245
Number of males (%)	870 (54.3%)	299,308 (55.3%)
Average age at discharge (males/ females)	59.2/ 70.5	76.6/ 79
Average length of stay (males/ females)	13.4/ 16.1	7.9/ 9.6
Number of deaths within 365 days of admission	188	54,499
Unadjusted death rates per 1,000 admissions (95% CI)	117.3 (101.4 – 135.0)	100.7 (99.9 – 101.5)

Table 8-5 - Characteristics of people admitted with a main diagnosis of CVD in 2007 and comorbid schizophrenia defined by recent discharge with main diagnosis of SCHIZOPHRENIA in the past year

	Main diagnosis of CVD and comorbid schizophrenia	No comorbid schizophrenia
Number of admissions	1125	716,431
Number of people	847	542,001
Number of males (%)	455 (53.7%)	299,727 (55.3%)
Average age at discharge (males/ females)	58.3/ 68.7	76.6/ 79
Average length of stay (males/ females)	8.7/ 12.1	7.9/ 9.7
Number of deaths within 365 days of admission	104	54,583
Unadjusted death rates per 1,000 admissions (95% CI)	122.8 (100.8 – 148.2)	100.7 (99.9 – 101.6)

Characteristics of people admitted with a main diagnosis of diabetes in 2007

There were 40,249 admissions for 31,332 people with a main diagnosis of diabetes between 1st January and 31st December 2007 in England. The ratio of 1.3 HES records per person where the main diagnosis was diabetes over one year is similar to than the ratio of 1.3 HES records per person shown in chapter 6 for SMI over the same time period. The demographic profile of the group is shown in Table 8-6.

Table 8-6 - Characteristics of people admitted with a main diagnosis of diabetes (DM) in 2007

	All admitted with a main diagnosis of DM (ICD10 codes E10 to E14)
Number of admissions	40,249
Number of people	31,332
Number of males (%)	17,295 (55.2%)
Average age at discharge (males/ females)	52.5/ 52.3
Average length of stay (males/ females)	7.6/ 7.3
Number of deaths within 365 days of admission	1,171
Unadjusted death rates per 1,000 admissions (95% CI)	37.4 (35.3 – 39.6)

Characteristics of people admitted with a main diagnosis of diabetes mellitus and comorbid SMI

Comorbidity with bipolar disorder and schizophrenia was slightly more common in people with a main diagnosis of diabetes mellitus. For example, of people admitted with a main diagnosis of diabetes mellitus, 0.2 - 0.3% had comorbid bipolar disorder depending on whether the diagnosis of bipolar disorder was noted as a secondary diagnosis on the same hospital record or if the diagnosis of bipolar disorder was recorded as the main diagnosis within the past year (see Table 8-7 and Table 8-8). Using the same criteria, 0.4 - 0.8% of people with diabetes had comorbid schizophrenia, (see Table 8-9 and Table 8-10).

The overall demographic characteristics of people with comorbid bipolar disorder or schizophrenia and a main diagnosis of diabetes did not vary substantial from people without comorbid SMI (see Table 8-7 to Table 8-10).

Table 8-7 - Characteristics of people admitted with a main diagnosis of DM in 2007 and comorbid bipolar disorder defined as secondary diagnosis of BIPOLAR DISORDER on the same hospital record

	Main diagnosis of DM and comorbid bipolar disorder	No comorbid bipolar disorder
Number of admissions	115	40,134
Number of people	87	31,245
Number of males (%)	38 (43.7%)	17,247 (55.2%)
Average age at discharge (males/ females)	54.3/ 57.2	52.5/ 52.3
Average length of stay (males/ females)	8.8/ 8.9	7.5/ 7.5
Number of deaths within 365 days of admission	3	1,168
Unadjusted death rates per 1,000 admissions (95% CI)	34.5 (8.8 – 93.8)	37.4 (35.3 – 39.6)

Table 8-8 - Characteristics of people admitted with a main diagnosis of DM in 2007 and comorbid bipolar disorder defined by recent discharge with main diagnosis of BIPOLAR DISORDER in the past year

	Main diagnosis of DM and comorbid bipolar disorder	No comorbid bipolar disorder
Number of admissions	80	40,169
Number of people	59	31,273
Number of males (%)	23 (39.0%)	17,263 (55.2%)
Average age at discharge (males/ females)	56.5/ 56.6	52.5/ 52.3
Average length of stay (males/ females)	14.6/ 7.3	7.5/ 7.5
Number of deaths within 365 days of admission	4	1,167
Unadjusted death rates per 1,000 admissions (95% CI)	67.8 (21.5 – 163.5)	37.3 (35.2 – 39.5)

Table 8-9 - Characteristics of people admitted with a main diagnosis of DM in 2007 and comorbid schizophrenia defined as secondary diagnosis of SCHIZOPHRENIA on the same hospital record

	Main diagnosis of DM and comorbid schizophrenia	No comorbid schizophrenia
Number of admissions	304	39,945
Number of people	236	31,096
Number of males (%)	133 (56.4%)	17,165 (55.2%)
Average age at discharge (males/ females)	47/ 58.5	52.6/ 52.3
Average length of stay (males/ females)	8.9/ 11.6	7.5/ 7.5
Number of deaths within 365 days of admission	6	1,165
Unadjusted death rates per 1,000 admissions (95% CI)	25.4 (10.3 – 52.9)	37.5 (35.4 – 39.7)

Table 8-10 - Characteristics of people admitted with a main diagnosis of DM in 2007 and comorbid schizophrenia defined by recent discharge with main diagnosis of SCHIZOPHRENIA in the past year

	Main diagnosis of DM and comorbid schizophrenia	No comorbid schizophrenia
Number of admissions	173	40,076
Number of people	134	31,198
Number of males (%)	73 (54.5%)	17,221 (55.2%)
Average age at discharge (males/ females)	48.5/ 53.6	52.5/ 52.3
Average length of stay (males/ females)	6/ 7.7	7.5/ 7.5
Number of deaths within 365 days of admission	7	1,164
Unadjusted death rates per 1,000 admissions (95% CI)	52.2 (22.8 – 103.3)	37.3 (35.2 – 39.5)

Unadjusted post-admission mortality rates

For all people with a main diagnosis of CVD, the mortality rate in the first 365 days after admission was 100.7 per 1,000 people admitted (95% CI: 99.9 – 101.6), see

Table 8-1. For people with comorbid bipolar disorder the mortality rate was lower than people without comorbidity at between 63.7 and 74.8 per 1,000 depending on the method chosen to select comorbid cases, see Table 8-2 and Table 8-3. On the other hand, for people with comorbid schizophrenia, the mortality rate was higher than people without comorbidity, see Table 8-4 and Table 8-5.

For all those with a main diagnosis of diabetes, the mortality rate in the first 365 days after admission was 37.4 per 1,000 people admitted (95% CI: 35.3 – 39.6), see Table 8-1. The mortality rate for people with the comorbid SMI was highly dependent on the method chosen to select comorbid cases, see Table 8-7 to Table 8-10.

Similar to findings shown by Abrams et al (2008), the unadjusted mortality rate for comorbid SMI was generally higher when comorbid cases were defined as having been discharged within the last year with a diagnosis of bipolar disorder or schizophrenia, than when comorbidity was defined as having a secondary diagnosis of bipolar disorder or schizophrenia on the same record (Abrams, Vaughan-Sarrazin et al. 2008).

Hazard rates adjusted for age and sex

From survival analyses summarized in Table 8-11, Table 8-12, and Figure 8-1 to Figure 8-8, after taking into account age and sex differences, comorbidity with bipolar disorder or schizophrenia was associated with higher mortality in people with a main diagnosis of CVD or DM, although only two results were statistically significant at the 5% level, and the findings were much less clear for people with a diagnosis of diabetes. For example, for people with a diagnosis of CVD and comorbid schizophrenia, the adjusted hazard ratio varied between 1.5 and 1.1 depending on the criteria used to select comorbid mental illness. In contrast, for people with a diagnosis of CVD and comorbid bipolar disorder, the adjusted hazard ratio varied between 0.9 and 1.5.

For people with a diagnosis of DM and comorbid schizophrenia, the adjusted hazard ratio varied between 1.7 and 1.4 depending on the criteria used to select comorbid mental illness. For people with a diagnosis of DM and comorbid bipolar disorder, the adjusted hazard ratio varied between 0.8 and 1.4.

Table 8-11 - Hazard ratios comparing the mortality risk in people with a main diagnosis of CVD with and without comorbid SMI, adjusted for age and sex

	Adjusted hazard ratio	
	Comorbidity defined as a secondary diagnosis of SMI recorded on the same hospital record	Comorbidity defined by recent discharge with a main diagnosis of SMI in the past year
Comorbid BIPOLAR DISORDER	1.5 (p = <.0001)	0.9 (p = 0.7)
Comorbid SCHIZOPHRENIA	1.1 (p = 0.1)	1.5 (p = 0.02)

Table 8-12 - Hazard ratios comparing the mortality risk in people with a main diagnosis of DM with and without comorbid SMI, adjusted for age and sex

	Adjusted hazard ratio	
	Comorbidity defined as a secondary diagnosis of SMI recorded on the same hospital record	Comorbidity defined by recent discharge with a main diagnosis of SMI in the past year
Comorbid BIPOLAR DISORDER	1.4 (p = 0.4)	0.8 (p = 0.8)
Comorbid SCHIZOPHRENIA	1.4 (p = 0.1)	1.7 (p = 0.2)

Figure 8-1 - Survival curves comparing admitted with a main diagnosis of CVD in 2007 and comorbid BIPOLAR DISORDER defined as secondary diagnosis of bipolar disorder on the same hospital record, adjusted for age and sex

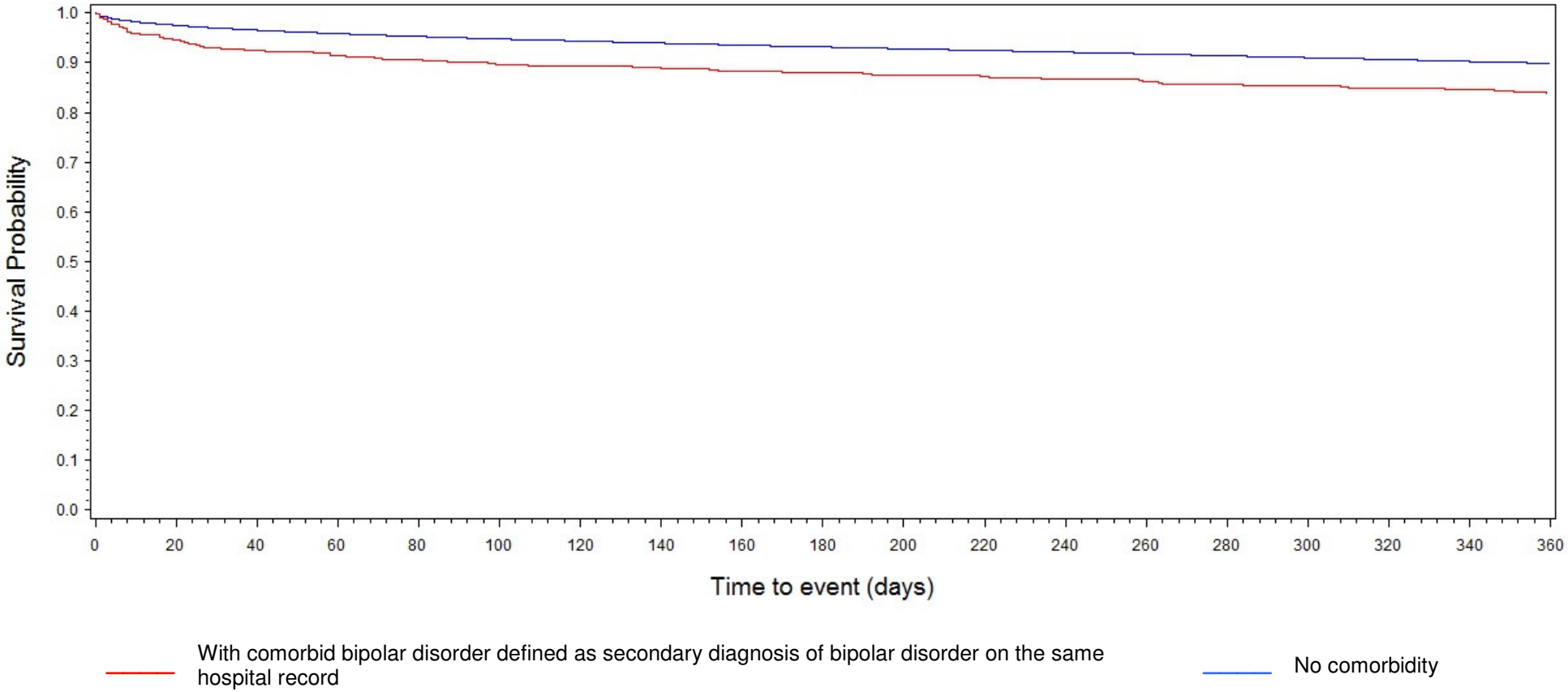


Figure 8-2 - Survival curves comparing admitted with a main diagnosis of CVD in 2007 and comorbid BIPOLAR DISORDER defined by recent discharge with main diagnosis of bipolar disorder in the past year, adjusted for age and sex

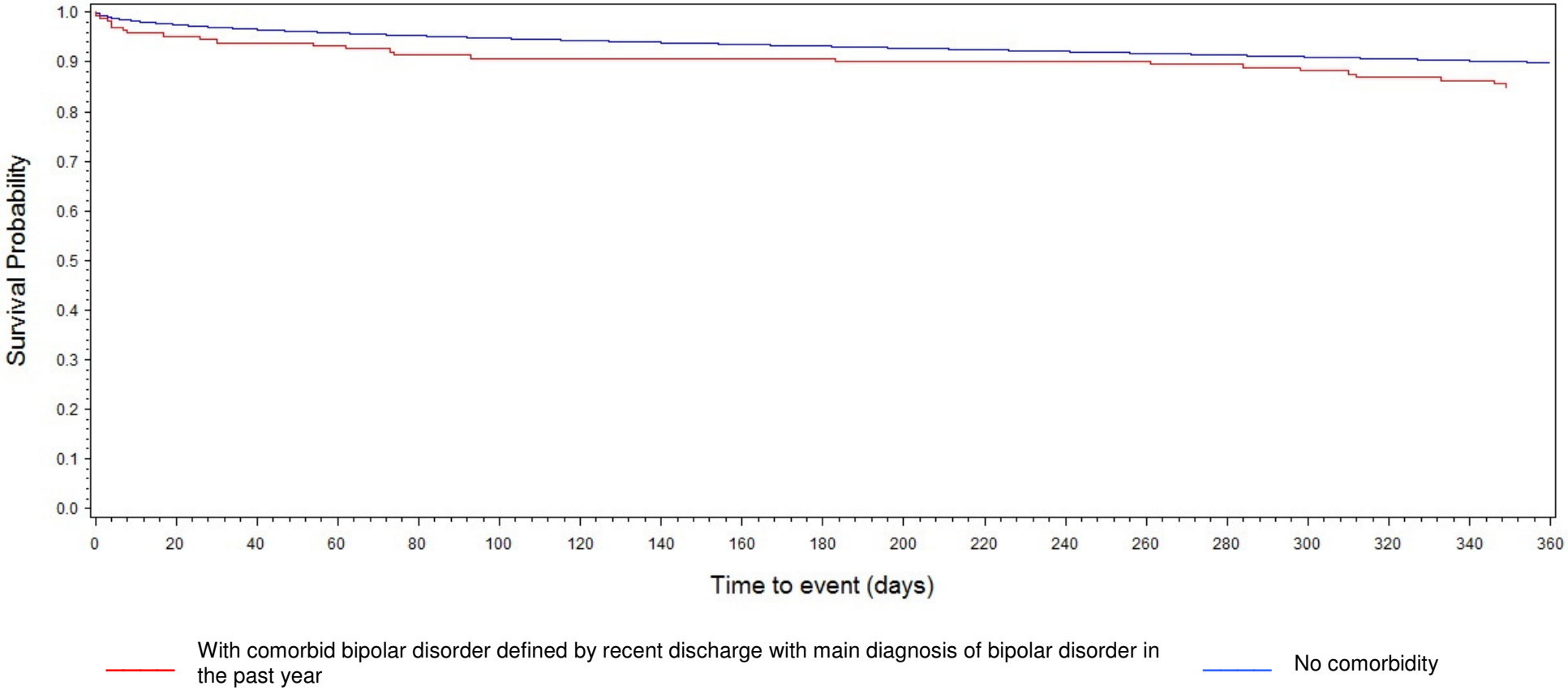


Figure 8-3 - Survival curves comparing admitted with a main diagnosis of CVD in 2007 and comorbid SCHIZOPHRENIA defined as secondary diagnosis of schizophrenia on the same hospital record, adjusted for age and sex

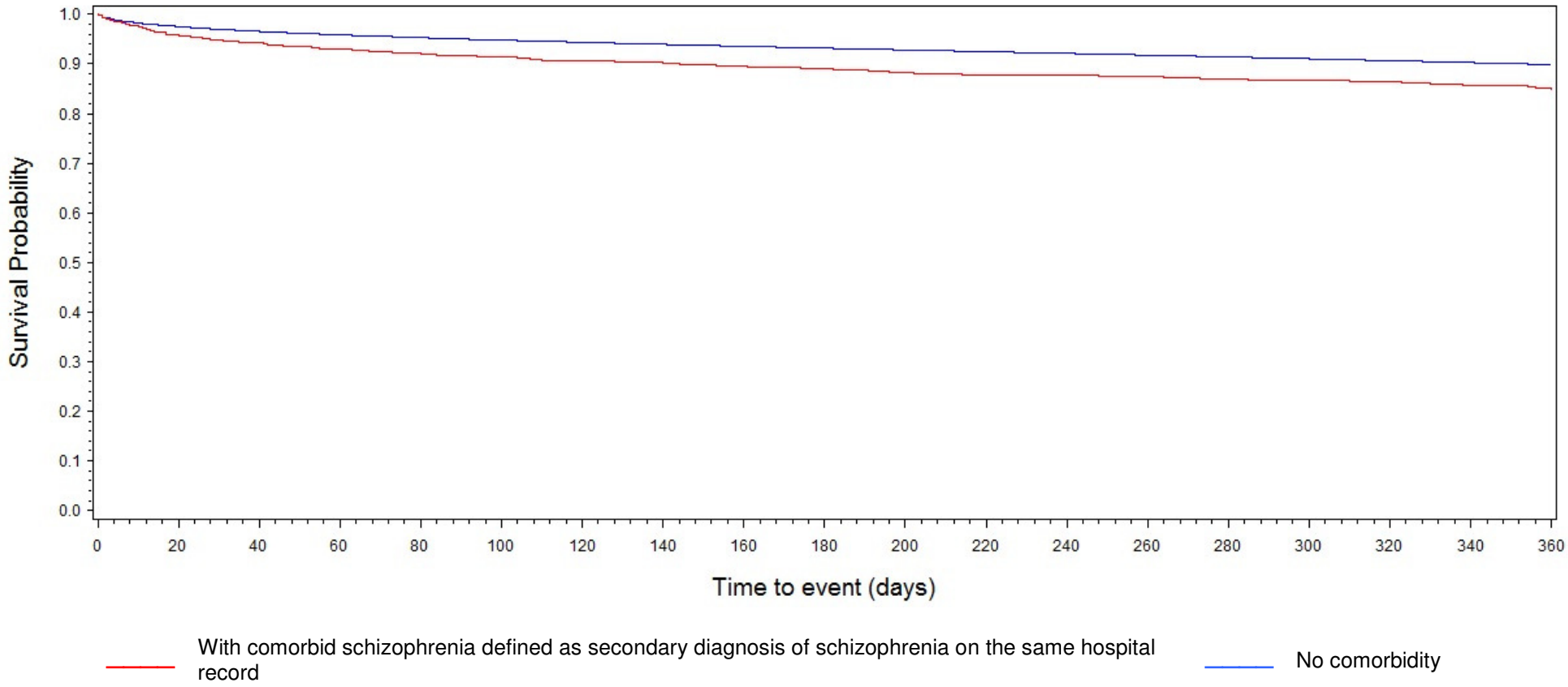


Figure 8-4 - Survival curves comparing admitted with a main diagnosis of CVD in 2007 and comorbid SCHIZOPHRENIA defined by recent discharge with main diagnosis of schizophrenia in the past year, adjusted for age and sex

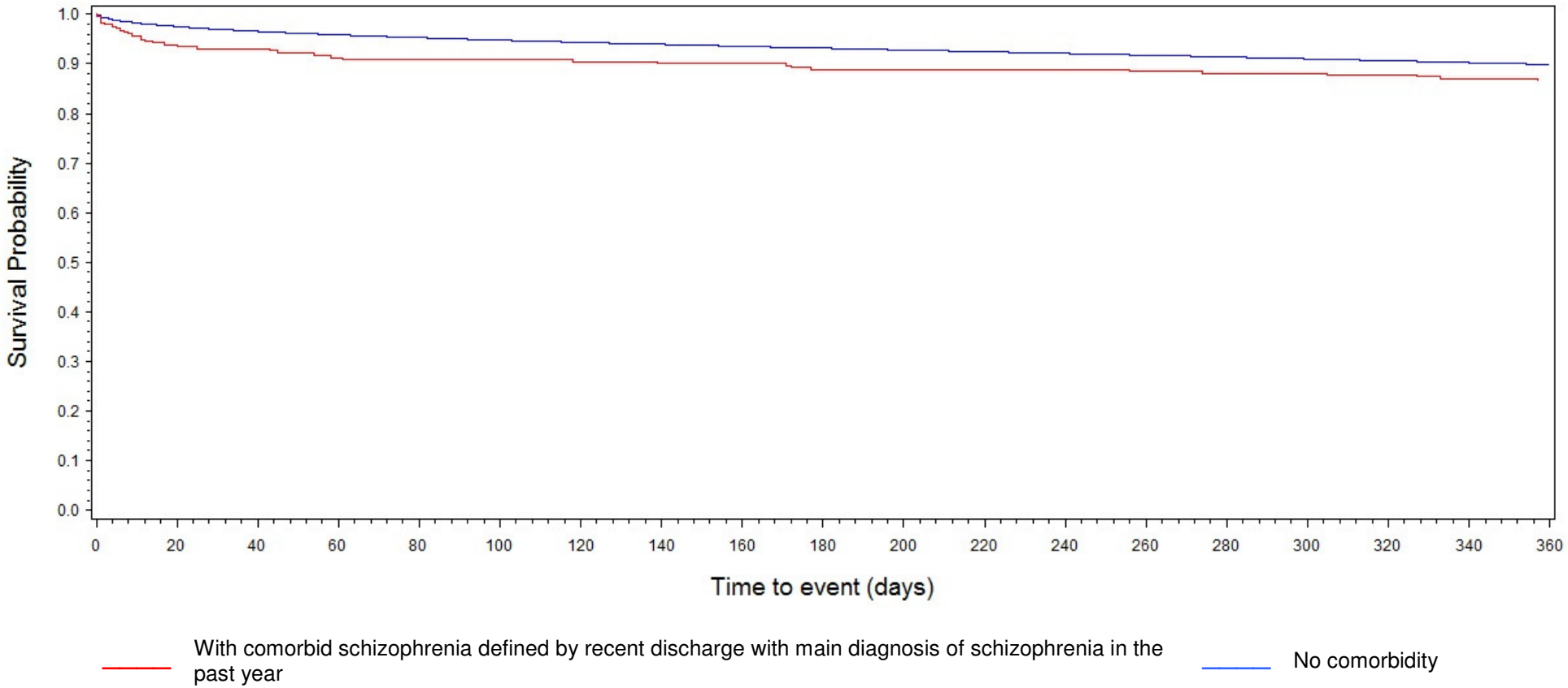


Figure 8-5 - Survival curves comparing admitted with a main diagnosis of DM in 2007 and comorbid BIPOLAR DISORDER defined as secondary diagnosis of bipolar disorder on the same hospital record, adjusted for age and sex

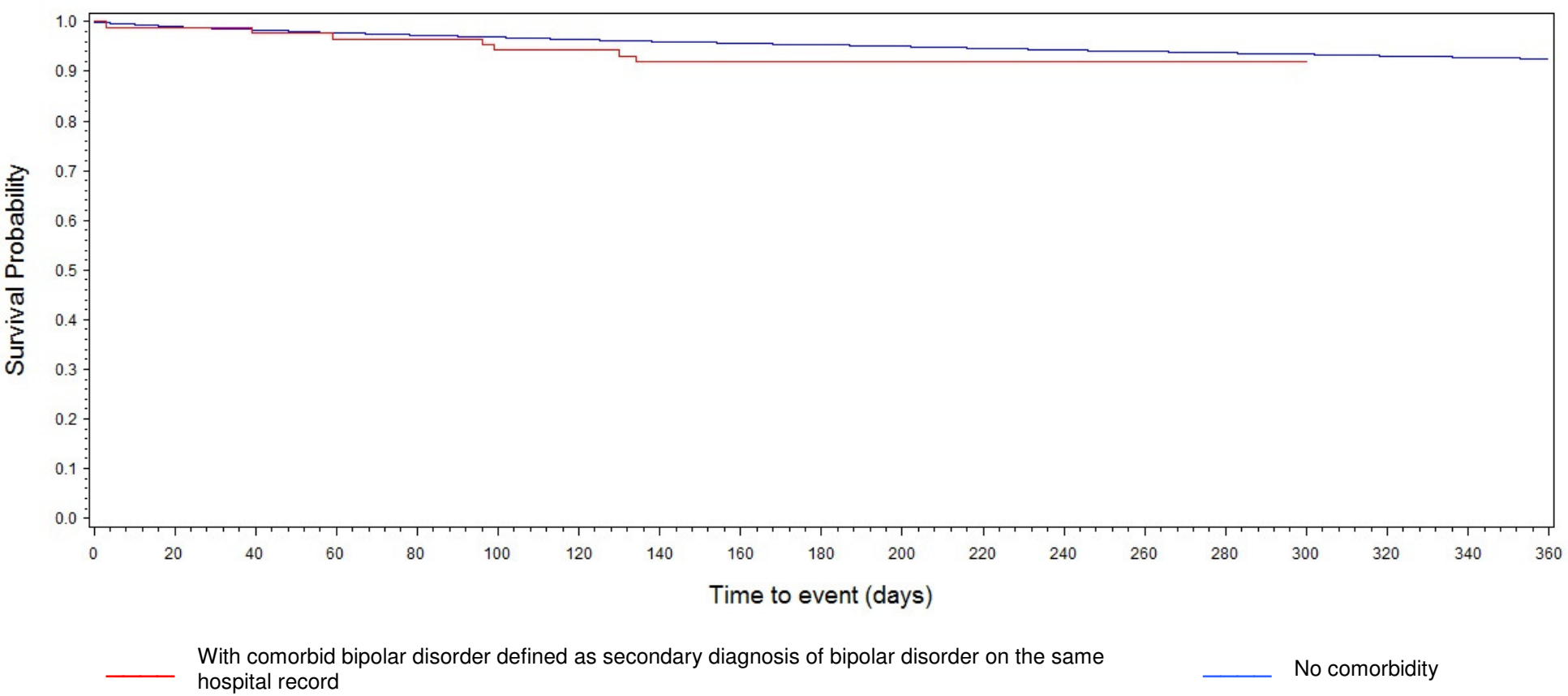


Figure 8-6 - Survival curves comparing admitted with a main diagnosis of DM in 2007 and comorbid BIPOLAR DISORDER defined by recent discharge with main diagnosis of bipolar disorder in the past year, adjusted for age and sex

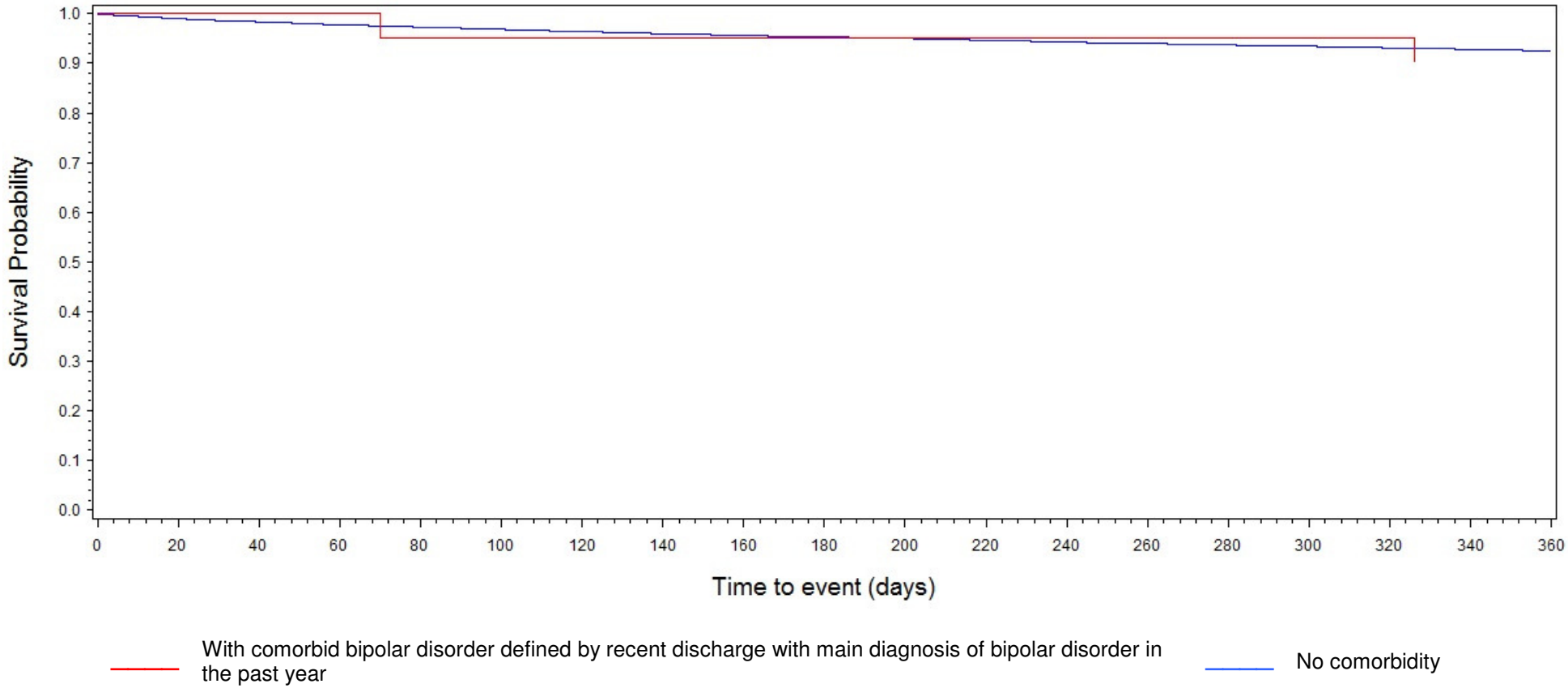


Figure 8-7 - Survival curves comparing admitted with a main diagnosis of DM in 2007 and comorbid SCHIZOPHRENIA defined as secondary diagnosis of schizophrenia on the same hospital record, adjusted for age and sex

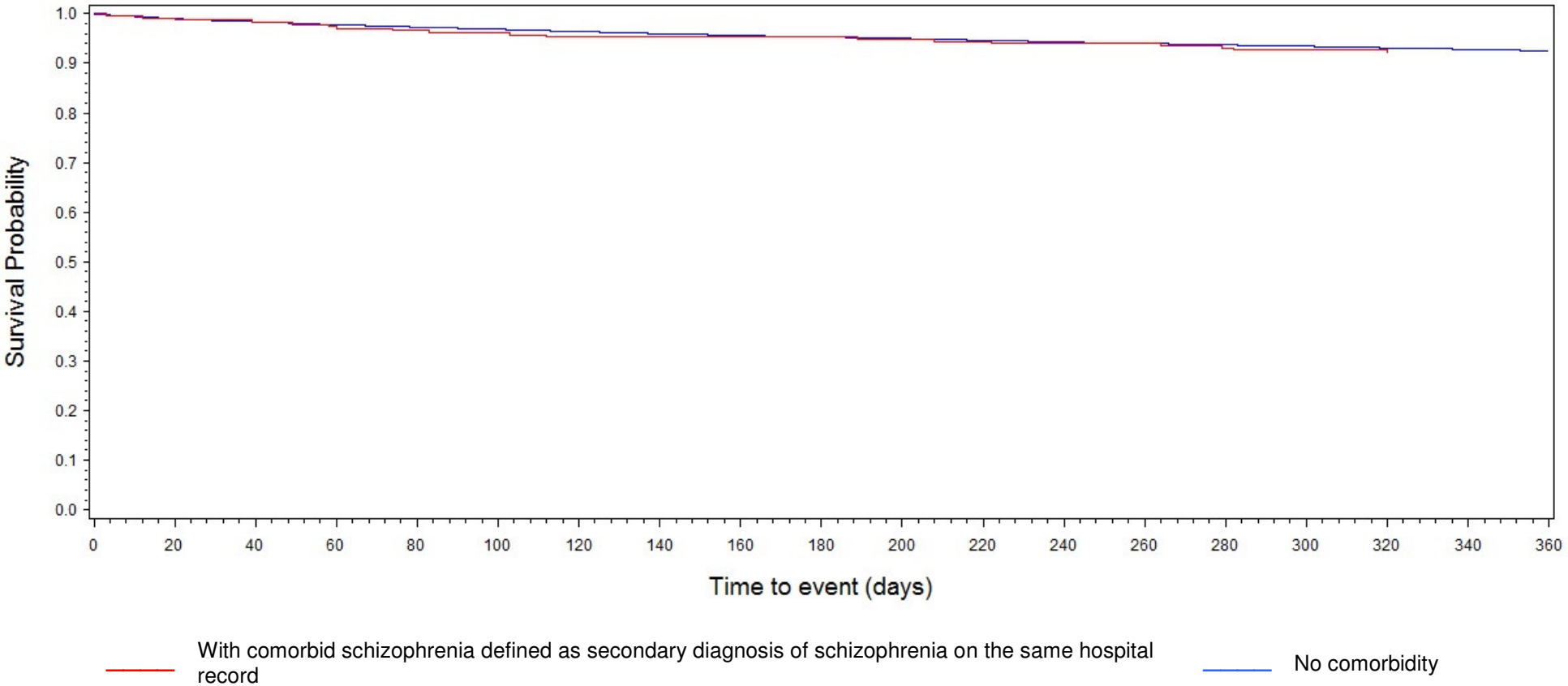
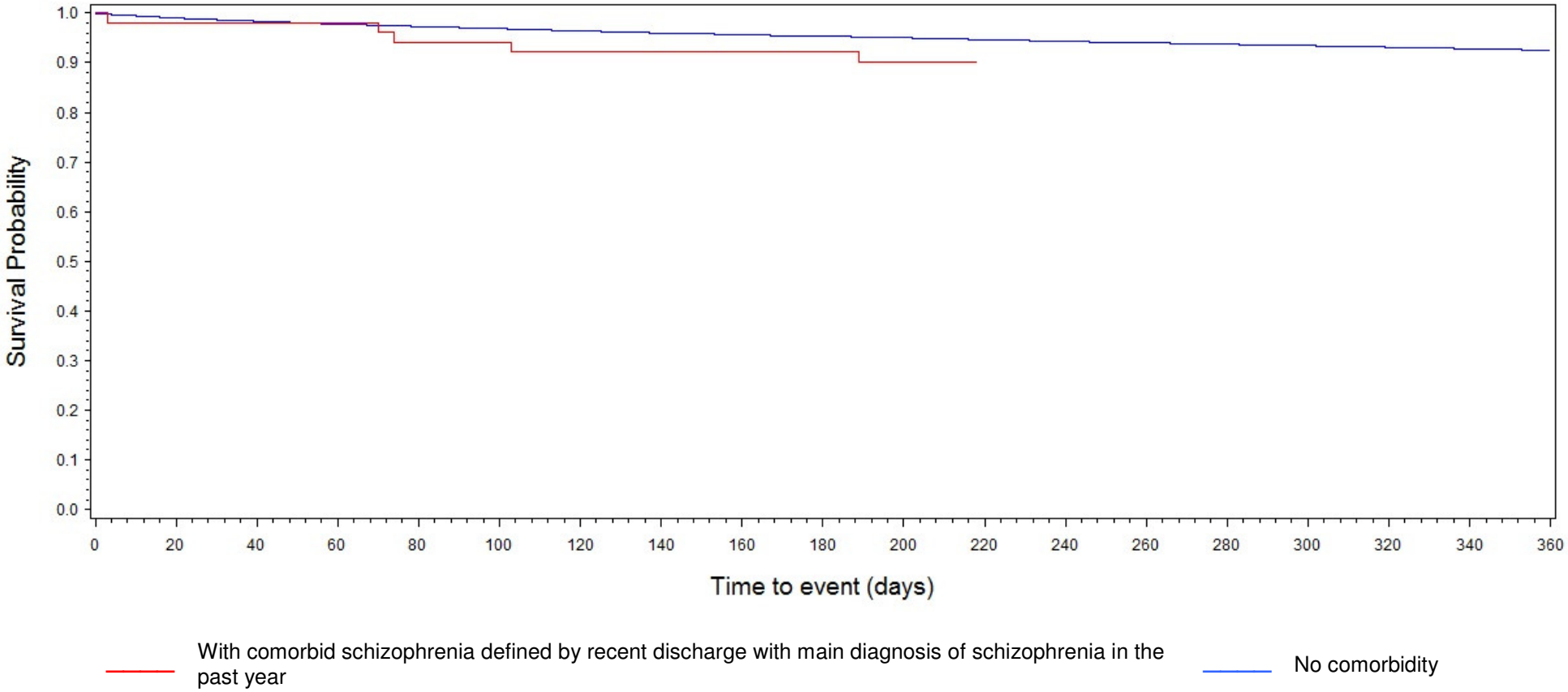


Figure 8-8 - Survival curves comparing admitted with a main diagnosis of DM in 2007 and comorbid SCHIZOPHRENIA defined by recent discharge with main diagnosis of schizophrenia in the past year, adjusted for age and sex



Summary of findings from chapter 8

The findings from this chapter showed that

1. Comorbidity with bipolar disorder or schizophrenia affects less than 1% of all admissions to inpatient care for CVD or diabetes. The exact level of comorbidity depends on the definition used.
2. Comorbidity with bipolar disorder or schizophrenia in people discharged with a primary diagnosis of cardiovascular disease or diabetes, has an important influence on mortality, although after adjustment for age and sex differences the results were not statistically conclusive.

Chapter 9 – Summary and Discussion

Key findings

In chapter 5 the following research questions were posed

1. Has the excess in all-cause mortality for people with bipolar disorder and schizophrenia increased or decreased over the last decade in England?
2. Is the mortality excess of the same magnitude for people with bipolar disorder and schizophrenia in England?
3. Is the trend in mortality consistent for people with bipolar disorder and schizophrenia of different ages and genders in England?
4. Is mortality for people with bipolar disorder and schizophrenia geographically consistent across England?
5. Does comorbid illness with bipolar disorder and schizophrenia in people with another main diagnosis, namely cardiovascular disease or diabetes, result in excess mortality?
6. To what extent are causes of excess deaths potentially avoidable in people with bipolar disorder and schizophrenia and therefore what would be the impact on the mortality excess of equalising those causes in England?

In this thesis the following details about the recent epidemiology of mortality in people with bipolar disorder and schizophrenia in England are presented to answer these questions.

The findings from chapter 6 confirm that the risk of death for people recently discharged from inpatient psychiatric care in England with a diagnosis of schizophrenia or bipolar disorder remains significantly higher than that of the general population. This excess all-cause mortality was observed for both discharge diagnoses although age- and sex-adjusted analyses indicated a greater magnitude of risk for schizophrenia, as indicated by a higher all-cause SMR. The results of specific-cause mortality analysis show that there was a greater excess of deaths from unnatural causes, such as accidents and suicides than natural causes, such as deaths from cardiovascular and respiratory diseases as evidenced by

greater specific cause SMRs in these populations. However, natural causes of death are much more numerous than unnatural causes, and hence the toll of mortality attributable to natural causes is the greater of the two overall. The results also show that age and gender are important determinants of the mortality gap, with young men who have a diagnosis of schizophrenia most at risk of death in the first year after discharge. Gender differences in the mortality gap for bipolar disorder were not evident. The mortality gaps described were not consistent across the country, with wide though non-significant geographical variation in the mortality gap observed. The underlying reasons for this variation are not explored in this thesis, but are likely to be multiple and complex given the many influences on mortality explained earlier.

The trend analysis shows that the mortality gap for people with bipolar disorder and schizophrenia had increased over the time period covered by the study.

Further investigation of the components of the increase in all-cause mortality excess over the study period showed that the trend had not been similar for both sexes, or different age groups, or for unnatural/ natural causes of death. Findings summarised in chapter 6 indicated that the mortality rate in some groups, especially people discharged with bipolar disorder or schizophrenia between the ages of 65 – 84 years is increasing, contrary to the overall mortality rate in both the general population and other people with the same condition. The results also showed that the increase in mortality was greater for men than for women with schizophrenia, resulting in a widening of the gender difference in the mortality gap over the course of the last decade. Trends in specific cause mortality suggested that the majority of the increase in the mortality gap was accounted for by deaths from natural causes, especially cardiovascular and respiratory diseases. The mortality gap due to unnatural causes such as suicide and accidental deaths on the other hand had remained reasonably stable over the years analysed.

Findings summarised in chapter 7 indicate that 'avoidable' causes of death are an important cause of death in people with bipolar disorder and schizophrenia and also a substantial contributor to the mortality gap seen in these populations. In cases under the age of 75 years, almost two thirds of all deaths within the first 365 days after discharge from inpatient care were found to be possibly avoidable. However calculation of hypothetical SMRs indicated that avoidable causes of death were not wholly responsible for the mortality gap in these populations, although interventions to reduce deaths from avoidable causes could reduce the mortality gap between these case groups and the general population appreciably, especially in people aged 45 years or below. In people with schizophrenia, reducing avoidable causes of death may also slightly narrow the gender difference in mortality. As mentioned, the hypothetical SMRs also indicate that reducing excess deaths classified as avoidable did not eliminate the mortality gap between these case groups and the general population. Even after discounting excess deaths from all causes classified as avoidable, people with schizophrenia under the age of 75 were still twice as likely to die as the general population in the first year after their discharge from hospital. This residual mortality was accounted for by unavoidable deaths across a broad range of disease groups.

Lastly, findings summarised in chapter 8 indicated that comorbidity with bipolar disorder or schizophrenia in people discharged with a primary diagnosis of cardiovascular disease or diabetes, had an important influence on mortality, although after adjustment for age and sex differences the results were not statistically conclusive. Comorbid illness with bipolar disorder and schizophrenia is an important consideration in characterising the epidemiology of mortality for cardiovascular disease or diabetes. However, more work needs to be done to accurately define comorbidity and identify people with comorbid disorders, as well as assessing the mortality amongst people who are admitted with a wider range of physical conditions and comorbid SMI to assess the totality of mortality risk from these severe mental disorders as comorbidity.

Methodological considerations, and strengths and weakness of this thesis (including the role of chance, bias, and confounding, and issues of causality)

The results in this thesis currently provide the most comprehensive and up to date estimates of the mortality gap for people with bipolar disorder and schizophrenia in England over the last decade. However the findings must be considered in the light of a number of methodological limitations of observational research designs, namely the role of chance or random error, the effects of bias or systematic error, as well as the role of confounding (Mann 2003; Zaccai 2004; Rothman, Greenland et al. 2008; Healy and Devane 2011).

Random error comes into play when the results of a study are governed by the laws of probability or chance, such as when the measure of effect in a study estimates the true population effect from a sample (Last 2006). As explained in chapter 4 the dataset used for this study contains a complete enumeration of all patients admitted to NHS care in England and, through linkage to national mortality data, a total national measure of mortality risk has been calculated in these vulnerable groups without the need to extrapolate from sample estimates. Thus the observed results are not derived from a sampling process and a role of chance is not applicable to these national data. These characteristics of the studies in this thesis aid the precision of the mortality estimates and generalisability of the findings compared with previous studies in the UK which have been limited to case registers within individual mental health trusts (Brown, Kim et al. 2010; Chang, Hayes et al. 2010) or within general practice registers (Osborn, Levy et al. 2007). However one should bear in mind that the measures calculated in this thesis relate to the mortality gap in the first year following hospital discharge over this time period only, and are not necessarily the same as the mortality risk experienced by people with bipolar disorder or schizophrenia outside these narrow parameters, notably people who have not recently been admitted for hospital care, and people who have been discharged for greater than one year.

Bias, namely the effect of systematic errors on the results from this study are possible for a number of reasons (Tversky and Kahneman 1974; Aschengrau and Seage 2003). First, as

explained earlier the selection of cases only who have been admitted for inpatient care and recently discharged in the last year is likely to have resulted in the systematic inclusion of a cohort of people with the most severe mental disorder given the fact that an increasing proportion of treatment for people with mild and moderate mental disorder now takes place outside the hospital setting (Bijl, de Graaf et al. 2003; Thompson, Shaw et al. 2004; Kessler, Demler et al. 2005).

In chapter 5, I mentioned how the extent to which the study populations in this thesis represents all people with bipolar disorder and schizophrenia could be gauged by comparing with information from other datasets such as the MHMDS and the QOF SMI register. Thus it is advisable that the conclusions from this thesis are limited to those who have been recently discharged with SMI and not to other population groups with SMI. However the degree to which selection bias has affected the results may also be quantified by comparing the results from this thesis with other studies that have selected cases from a community sample. For example, Joukamaa and colleagues found an SMR for CVD in a community sample of people from Finland in 2001 with a diagnosis of schizophrenia of between 1.6 and 2.9 for women and men respectively. Whilst David Lawrence and colleagues found an SMR for CVD of between 0.9 and 1.7 for women and men respectively from a community sample of people from Australia in 2003. This compares with an SMR for CVD of 2.5 found in this thesis in people recently discharged with schizophrenia in England in 2006 (Joukamaa, Heliovaara et al. 2001; Lawrence, Holman et al. 2003; Osborn, Levy et al. 2007). Amaddeo and colleagues directly compared mortality from a cohort of people with SMI who had attended outpatients only (SMR=1.3) and inpatients (SMR=2.2) as well over the course of their study in 1980-90s and found a substantial difference in the SMRs (Amaddeo, Bisoffi et al. 1995).

Second, reliance on routinely collected records has a number of advantages and disadvantages for epidemiological research which are well known (Glover 2003; Mann 2003; Rothman, Greenland et al. 2008; Perera, Soremekun et al. 2009), and listed in Table 9-1. An important limitation of routinely collected hospital records that could be a source of bias is the

completeness and accuracy of diagnostic codes used to identify people with a main or comorbid diagnosis of bipolar disorder or schizophrenia. The extent of measurement bias due to the miscoding of the diagnosis could be assessed by comparing accuracy of hospital records with the recording of cases using gold standard diagnostic tools, although the extent of bias due to the incompleteness of data is harder to quantify. A recent systematic review of hospital diagnostic coding accuracy by Burns and colleagues in England suggested that the main diagnosis is over 80% accurate for a range of conditions compared with gold-standard diagnosis, although the accuracy of bipolar disorder and schizophrenia diagnoses were not specifically tested (Burns, Rigby et al. 2011). According to a recent report by the Audit Commission in the UK, the secondary diagnosis is approximately 70% accurate across a range of conditions (Spencer 2011). However any measurement error due to the poor ascertainment of cases or miscoding of hospital records is likely to result in non-differential information bias, unrelated to the outcome as the data was collected before death. This is likely to result in no change in the mortality risk compared with the general population, or an under-estimate of the true result due to cases of bipolar disorder or schizophrenia being missed from the study.

With regards to the study of trends in psychiatric epidemiology, routinely collected data also has the disadvantage that it may be influenced by trends and fashions in the recording of certain symptoms and diagnosis (Paris 2004; Baca-Garcia, Perez-Rodriguez et al. 2007), as well as changes to diagnostic classification criteria. During this study the clinical coding of national hospital records was consistent using ICD10, however the coding of deaths changed from ICD9 to ICD10 between 1999-2000. Changes in diagnostic fashions are harder to identify. These changes may limit the comparisons of different cohorts over time, however the nature of these measurement biases are difficult to predict, although they may be estimated by using different range of codes to select cohorts of people with bipolar disorder and schizophrenia, and specific causes of death.

The measurement of outcomes in this thesis may also be influenced by bias. All-cause mortality is likely to be complete and accurate given the statutory requirement to record all deaths in the UK. However specific cause mortality including the enumeration of avoidable causes of death are likely to be influenced by the recording practices of clinicians (Nielsen, Bjornsson et al. 1991; Maudsley and Williams 1993). For example previous evidence has shown that psychiatric conditions are rarely mentioned as the primary cause of death and more often mentioned elsewhere on the death certificate if at all (Goldacre, Duncan et al. 2006). In fact it is estimated that only 5% of deaths in people with a diagnosis of schizophrenia are recorded as having such on their death certificate in the UK (Brown, Kim et al. 2010). However, the analyses in, and conclusions in, this thesis do not depend on the accurate identification of the mental illnesses on death certificates. A specific issue in the study of mortality in people with mental illness is the possibility that death in a person with a previous diagnosis of mental illness or recent contact with mental health services may be scrutinised more thoroughly than other deaths (Robinson, Meehan et al. 2002; Swinson, Ashim et al. 2007). This may include the need for a coroner's investigations and may result in a delay in the recording of deaths and differential recording of some mortality outcomes in these groups, such as suicide resulting in higher specific-cause mortality for these groups compared with the general population.

The quality and completeness of routinely collected records, may also affect the precision of data linkage, causing differential bias in trend studies. As mentioned in chapter 5, whilst changes in the recording of diagnosis, and variables used for data linkage may not affect studies done over a short period of time, studies done over longer periods of time may be affected by changes in the recording of diagnosis and the quality of data linkage in routinely collected linked databases. Data from the NHS Information Centre and HESOnline, showing an improvement in the recording of valid NHS numbers on HES records over the last decade from 83.2% in 2000-01 to 96.8% in 2008-09 (2009) suggests that it may have been easier to identify records belonging to the same person later in the file than earlier on. Thus the quality of data linkage over the course of the 13 year file may have increased as suggested by the

ratio of HES records to people in the 13 year file of approximately 3.6 HES records per person compared with an earlier 5 year file which had a ratio of approximately 2.3 HES and death records per person (Gill 2004). This may result in more linked death records being identified towards the end of the datafile than at the start, and may cause an inflation of all post-discharge mortality rates. Equally, if more records were assigned to each person, namely more readmissions were identified then the counting methods used in this thesis, namely counting only the first admission in a study period and ceasing follow-up when there is a readmission for any diagnosis or death, (described more fully in chapter 6) would be expected to decrease the number of deaths included and deflate all post-discharge mortality rates. The degree and direction of bias in mortality trends caused by these two competing factors is difficult to predict.

A third potential source of bias is from the use of definitions of natural/ unnatural mortality, and avoidable/ unavoidable deaths to group together specific causes of death. I have discussed the pros and cons of using definitions of avoidable mortality in populations with SMI in chapter 7. Essentially enumeration of specific causes of death is dependent on the accurate recording of specific causes of deaths which is known to be imprecisely recorded (Smith Sehdev and Hutchins 2001; Flaxman, Vahdatpour et al. 2011). This is likely to cause a non-differential bias, however, if a definition of specific cause mortality includes only those deaths that are better recorded in people with SMI, then specific cause mortality would be systematically over-estimated in this group. This may occur for example with the recording of unnatural deaths in people with SMI, especially if the clinician completing the death certificate is not blinded to the diagnosis of the patient. This would cause a differential bias and a falsely higher mortality rate in those with SMI.

Bias as a result of the use of categories to classify specific causes of death cannot be absolutely excluded, however it is difficult to predict in which direction the biases will operate on the morality risk estimates.

Lastly, the use of persons rather than person-time as the denominator in my analysis to calculate mortality rates and SMRs may have resulted in measurement bias as individuals in the study group would have been at risk for different lengths of time, i.e. the study population was dynamic. The calculation of mortality rates use in this study involves counting the total number of individuals in the population at the start of the study. This is then used as the denominator for calculation of mortality rates. Person-years analysis involves calculating the exact time each individual spends in the study before developing the outcome of interest and using person-time as the denominator (Rothman, Greenland et al. 2008). For the calculation of SMRs, the use of person rather than person-years as the denominator in the calculation of mortality rates assumes that on balance each individual in the study population spends the same amount of time in the study. This is more likely to cause bias when the study population is not in a steady state, namely the number of people entering the population is not balanced by the number exiting the population in any period of time within levels of age, sex and other determinants of risk (Rothman, Greenland et al. 2008). In the calculation of SMRs the use of person denominator may cause bias when the period of risk for the study population is systematically different from the period of risk in the comparison population used to calculate the SMRs. For example if people with SMI had spent less time in the study group before they died as opposed to the time recorded in the general population, then the use of person as opposed to person-years as the denominator may have adversely inflated the mortality rate in the study population with SMI, thus artificially inflating the SMRs.

Residual confounding, or the distortion of the estimated effect of an exposure on an outcome caused by the presence of an extraneous factor associated with both the exposure and the outcome (Last 2006) is possible given the complex relationship between severe mental illness and mortality shown in Figure 1-1, and. the limitation of routine health records used in this thesis. Important confounders, and explanatory variables to be considered in the analysis, including drug and alcohol use, socio-economic status, smoking status, dietary consumption, and physical exercise as well as the severity of the physical illness are not recorded.

Table 9-1 - Strengths and weaknesses of routinely collected data for epidemiological research

Strengths	Weaknesses
Readily available	Delay between collection and publication, especially for mental health research where there is often a lengthy delay with deaths needing to be referred to the coroner
Often standard variables are available across the country	Equivalent data not always available for all countries
Low cost to obtain and use for research purposes	Data may not be collected in a uniform way across the entire population, thus causing measurement bias
Linkage to other datasets can enlarge the number of variables within the research dataset, compared to the administrative dataset, and allow many more research questions to be addressed including physical health in those with mental illness, which may not be answered with information from psychiatric registers used on their own	Data is not primarily collected for research purpose thus data quality, including reliability of diagnoses, and missing data may result in potential selection and measurement biases. Information on important co-variates is often missing or of variable quality
Modern encryption methods have improved data security	Where there are small numbers of cases, it may be possible to identify individuals, threatening confidentiality

Reconsideration of the key findings in relation to the background literature

1. What do the findings tell us about the recent epidemiology of mortality in people discharged from inpatient care with bipolar disorder and schizophrenia?

People with bipolar disorder and schizophrenia are known to be at high risk of death. Similar to the findings in this thesis, previous studies have shown that people with schizophrenia have a slightly higher risk of death, and that age (Laursen, Munk-Olsen et al. 2007; Chwastiak and Tek 2009; Tiihonen, Lonnqvist et al. 2009; Lawrence, Kisely et al. 2010) , sex (Hoye, Jacobsen et al. 2011), and geographical location (Kiviniemi, Suvisaari et al. 2010) are important determinants of mortality. However this is the first time that data for the whole of England has been used to quantify the mortality gap from all causes in all people discharged from inpatient care with a diagnosis of bipolar disorder and schizophrenia (see

Table 2-1). This is also the first time that mortality risk has been explored by geographical location in England. Taking into account the methodological considerations mentioned above, the large size of the studies included in this thesis aids the generalisability of the findings.

Specific causes of death in people with a diagnosis of SMI have been described before, especially the higher risk of death from unnatural causes including accidents and suicide (Goldacre, Seagroatt et al. 1993; Harris and Barraclough 1997; Hall, O'Brien et al. 1998; Hiroeh, Appleby et al. 2001; 2002; 2002; Gau and Cheng 2004; Dutta, Boydell et al. 2007; Simon, Hunkeler et al. 2007), as well as some natural causes such as cardiovascular and respiratory disease (Goldacre, Seagroatt et al. 1993; Harris and Barraclough 1997; Hall, O'Brien et al. 1998; 1999; Hiroeh, Appleby et al. 2001; Osby, Brandt et al. 2001; 2002; 2002; Gau and Cheng 2004; Goff, Cather et al. 2005; Tsai, Lee et al. 2005; 2008; Hiroeh, Kapur et al. 2008; Roshanaei-Moghaddam and Katon 2009; Chang, Hayes et al. 2011). These findings are also replicated in this thesis, showing that age and sex are important determinants of death from specific causes as well as all causes.

The findings that a majority of the mortality gap is a result of avoidable causes of death amongst people with bipolar disorder and schizophrenia is similar to recent findings by Amaddeo in Italy (Amaddeo, Barbui et al. 2007) and Rasanen in Finland (Rasanen, Hakko et al. 2005), however they are the first in England using data collected in the past decade. Brown and colleagues had previously reported an SMR for avoidable causes of 4.7 in people with a diagnosis of schizophrenia followed up between 1981-95. In this thesis, a similar SMR of 5.4 was found for people under the age of 75 discharged with a diagnosis of schizophrenia in 2006-07. This finding suggests that there may have been an increase in avoidable causes of death in the past decade, although the findings are difficult to compare directly as the definitions of avoidable deaths and the age groups used in the two studies are slightly different.

2. What do the findings tell us about the recent trends in mortality amongst people discharged from inpatient care with bipolar disorder and schizophrenia over the last decade?

Mortality trend analysis confirmed that the mortality gap for people recently discharged with a main diagnosis of bipolar disorder and schizophrenia compared with the general population, has not narrowed in the past decade in England.

However trends in mortality are inherently difficult to study especially using routinely collected data because in addition to the methodological issues associated with studying SMI mentioned above, there are also difficulties associated with consistently collecting repeated diagnostic and outcomes measures, as well as important covariates and confounders over long periods of time (Miller 2011). For example as mentioned above the consistent collection of NHS number is important in determining the quality and consistency of data linkage and minimising bias.

In addition one needs to be careful about the interpretation of trends as they can be confounded by unmeasured variables such as changes in admission threshold for inpatient care over the study period. For example if mortality is related to the severity of mental illness the findings of increasing SMRs over time in this thesis may be confounded by a change in admission thresholds that results in more severely disturbed people being admitted over time. This would increase the mortality gap measured in the inpatient population, compared with the mortality gap measured in the total population with SMI as a whole. To some extent this could have been addressed by taking account of differences in disease severity in SMR analysis and taking account of changes in admission thresholds in trend analyses (Thompson, Shaw et al. 2004). However stratified analysis by disease severity was not possible as information on severity is not collected within the dataset used in this thesis and other studies have suggested that there is not a direct relationship between the severity of mental illness as measured by symptomatology and risk of death (Hayes, Chang et al. 2012).

Residual confounding from severity of illness cannot be excluded entirely and the finding of reductions in discharges over the period covered by this thesis suggests that there may have been some concentration of mortality risk in these hospitalised cohorts which could account for the widening mortality gap. Any subsequent research should aim to control for disease severity and take account of changing patterns of admission over time, for example by including data from the MHMDS which includes information on inpatient, outpatient and community treatment services.

Bearing in mind the methodological considerations and need for caution in interpreting these results, then the observed upward trend in mortality is similar to trends in a number of other countries (Saha, Chant et al. 2007) although again caution must be taken in comparing these studies directly as they are similarly subject to biases, residual confounding, and other problems of measuring mortality trends. However, Saha and colleagues undertook a systematic review and meta-analysis of 37 mortality studies in people with schizophrenia from 25 countries, including the UK between 1980 and 2006, and found that the all-cause SMR was 2.6 during this period (Saha, Chant et al. 2007), which is similar to findings in this thesis of an SMR of 2.2 for people discharged with schizophrenia in 2006. This is compared with two meta-analysis conducted by Brown and colleagues using 18 studies from 8 countries, between 1969 and 1996 and by Harris and Barraclough examining data from 20 studies conducted between 1973 and 1995 which both showed an all-cause SMR of 1.5 (Brown 1997; Harris and Barraclough 1998), suggesting that there has been a widening of the mortality gap over the last decades. In contrast to Saha, the findings from this thesis showed that in England the mortality gap has widened over the past decade in specific age groups, especially people over the age of 65 years and for specific conditions such as deaths from cardiovascular and respiratory disease rather than across the board for people with bipolar disorder and schizophrenia.

A more recent large cohort study of 66,881 people with schizophrenia from Finland between 1996 and 2006 by Jari Tiihonen and colleagues however suggests that there has been no

widening of the mortality gap over time in Finland, although this study was based on a community sample, rather than an admitted sample of people (Tiihonen, Lonnqvist et al. 2009).

The finding of a widening mortality gap in a number of countries worldwide suggests that there may be common factors underlying the trends in mortality that are not restricted to one country.

One potential explanation for the findings is the increasing use of second-generation anti-psychotic medications, which has been seen over the past decade in many countries (Santamaria, Perez et al. 2002; Aparasu, Bhatara et al. 2005; Caceres, Penas-Lledo et al. 2008; Ilyas and Moncrieff 2012) and particularly prescribing of these medications to the elderly in the UK (Fossey, Ballard et al. 2006; Banerjee 2009). Evidence of adverse effects of these medications has been suggested (Cheng-Shannon, McGough et al. 2004; Lee, Gill et al. 2004; Najjar, Welch et al. 2004; Aparasu and Bhatara 2005; Rapoport, Mamdani et al. 2005; Citrome 2007; Chahine, Acar et al. 2010; Leon, Gerretsen et al. 2010) especially amongst the elderly who may be more susceptible to risk effects from these drugs (Citrome 2007; Leon, Gerretsen et al. 2010) which may explain some of the mortality trends seen. However the adverse effects of second-generation anti-psychotic medications has been contested (Jones, Barnes et al. 2006; Lewis, Davies et al. 2006) and the hypothesis relating to their effects on mortality trends must be answered in future research using information on prescribing trends for populations with SMI. This information is available from community datasets such as the GPRD or from some psychiatric case registers such as that held by the South London and Maudsley NHS Trust.

Another possible explanation is a change in the management practices for people with SMI with the use of less aggressive drug treatments, more emphasis on psychosocial management, and the use of medication free periods to minimise the occurrence of adverse effects from anti-psychotics, and increase compliance with treatment (Calton and Spandler

2009). In recent years, early intervention services have attempted to identify people with a first episode of psychosis as early as possible, reducing the duration of untreated psychosis and changing the timing of delivery of interventions (Tiffin and Glover 2007; Francey, Nelson et al. 2010). However some have questioned whether short periods, medication free, in early the stages of an episode of schizophrenia can result in demonstrable long-term on morbidity and mortality (Carpenter 1997). Again this hypothesis cannot be directly tested in this thesis and further work should be done to test this using other data sources.

As discussed earlier, trends in deinstitutionalisation of psychiatric care and changing hospital admission patterns during the study period could also influence the type of people admitted for inpatient care, resulting in the mortality trends seen.

Lastly the mortality trends may be a result of a more general changes in health service policy and delivery over the last decade, including a move to the provision of healthcare services in the community and primary care could also explain the findings, especially in the context of socially isolated, disabled service users who may have difficulty accessing healthcare services (Foundation 2010; Meltzer, Bebbington et al. 2013). For example Patterson and others have demonstrated that self-reported loneliness is a risk factor for all-cause mortality, mortality from ischemic disease and mortality from other cardiovascular diseases, independent of other risk factors (Patterson and Veenstra 2010; Luo, Hawkley et al. 2012).

The mortality trend has not been of consistent magnitude for all countries (Saha, Chant et al. 2007) which would suggest that local factors are also important in determining the trend in mortality. For example geographical differences in anti-psychotic prescribing have been described (Masand, Arora et al. 2001; Owen, Feng et al. 2001; Hayhurst, Brown et al. 2003). Other local factors include geographical differences in healthcare provision (Philo 1997; Bindman, Glover et al. 2000; Philo 2005; Edlund, Belin et al. 2006), differential access to physical and mental healthcare (Lawrence and Kisely 2010), differences in treatment

practices including follow-up care, and differences in the prevalence of comorbid alcohol/ substance abuse (Luty 2002; Edlund, Belin et al. 2006).

Bradford-Hill's criteria for causation (Hill 1965) can be used to assess the possible causative factors shown in Figure 1-1 involved in the mortality trends. These criteria provide a logical structure for investigating and defining causality in epidemiological studies (Ward 2009), and Swaen had offered a method to quantify the weight of evidence for a causal association (Swaen and van Amelsvoort 2009), see Table 9-2.

Table 9-2 - Bradford Hill criteria

Strength of association – i.e. the stronger the statistical association, the greater likelihood of causal effect
Consistency – i.e. when results are replicated in studies in different settings using different methods
Specificity – i.e. when a single putative cause produces a specific effect
Temporal relationship – i.e. where exposure always precedes the outcome.
Biological gradient – i.e. where an increasing amount of exposure increases the risk.
Plausibility – i.e. where the association agrees with currently accepted understanding of pathological processes
Coherence – i.e. the association is compatible with existing theory and knowledge
Experiment – i.e. the condition can be altered (prevented or ameliorated) by an appropriate experimental regimen
Analogy – i.e. the extent to which other possible explanations have been taken into account and have effectively ruled out

3. What do the findings tell us about the impact of comorbidity with SMI on mortality?

The finding that comorbidity with SMI in people admitted primarily with cardiovascular disease or diabetes results in increased mortality has been shown previously by other researchers including Lesperance and others who found increased mortality in people with CVD and depression (Lesperance, Frasure-Smith et al. 2000; Blumenthal, Lett et al. 2003), although this is the first time it has been shown for people with comorbid bipolar disorder and schizophrenia in England over the last decade. However the findings are at odds with the lower mortality found by Abrams and colleagues amongst people with CVD and comorbid SMI more generally (Abrams, Vaughan-Sarrazin et al. 2008; Abrams, Vaughan-Sarrazin et al. 2009; Abrams, Vaughan-Sarrazin et al. 2010). These differences may be explained by the different techniques used to select comorbid psychiatric disorder, which has a considerable impact on the estimate of mortality risk as shown in this thesis and previously by Abram and colleagues (Abrams, Vaughan-Sarrazin et al. 2008). It may also be explained by the residual differences in socio-economic status, smoking, dietary consumption, and physical exercise as well as the severity of the physical illness between those with and without SMI that were not accounted for in the analysis and may have affected the risk of death.

Further research on mortality in people with co-,morbid bipolar disorder or schizophrenia, especially controlling for the factors mentioned above, may reveal whether comorbidity is an important contributor to mortality from these conditions. It may also reveal whether the same pathophysiological mechanisms involved in causing mortality in people with a main diagnosis of bipolar disorder or schizophrenia would be involved in mortality in people with comorbid bipolar disorder or schizophrenia, as little research has been conducted on this subject thus far.

4. What do the findings tell us about the possible impact of interventions to reduce mortality, especially those deaths that are considered avoidable?

The use of hypothetical SMRs allow us to quantify the scope for public health and health services interventions to reduce the mortality gap between people with SMI and the general population. As mentioned above, a similar technique has been used in the field of demography to quantify the maximum extent of longevity of human life using estimates of the extent of 'exogenous', i.e. deaths as a result of external or modifiable causes, and 'endogenous', i.e. deaths as a result of internal or non-modifiable causes (Olshansky 1992). However this is the first time that this technique has been used to estimate the contribution of 'avoidable' deaths, namely those that are 'amenable' to high quality medical services and those that are 'preventable' through public health interventions (Wheller, Baker et al. 2007). It is also the first time these estimates have been undertaken in populations at high risk of death in England, namely people with SMI. The findings suggest that current medical and public health technologies could have a large effect on reducing the mortality gap, decreasing this gap by almost two-thirds, which is an important message for health care policy makers. However the findings also suggest that the effect of unavoidable deaths across a broad range of disease groups still requires further research.

Implications

Areas for further research

The results in thesis reinforce the need for further research in this area in the UK, as the mortality gap has not decreased and is increasing in some groups such as those over the age of 65. Further research is needed to investigate the contribution of possible important explanatory variables such as anti-psychotic medications, drug and alcohol use, smoking, dietary consumption, physical exercise and access to healthcare services on the mortality trend over the past decade. Future studies should also aim to collect information on important confounders such as social and economic deprivation, and illness severity, to allow their effects to be quantified and appropriately controlled. Detailed sub-studies need to be undertaken on those groups with particularly high risk of death, including older people (>65 years old) with SMI who appear to have experienced the most substantial increases in excess mortality over the studied period, as well as people with respiratory and cardiovascular disease whose deaths appear to form the majority of the excess.

There is also a need to investigate the burden the death from unavoidable causes, in order to better characterise these deaths and offer remedial solutions. This work may need to go hand-in-hand with refining current definitions for avoidable mortality for populations with SMI, as the definitions used in this thesis are applicable to the general population which has a different mortality experience from these sub-groups. An example is the use of ICD10 codes U00 to U99 (codes for special purposes) which are recorded widely on the death certificates of patients with a previous admission for SMI but which are not considered 'avoidable'. Codes U00 to U99 are new to ICD10 4th edition, which is reserved for the provisional assignment of new diseases of uncertain aetiology (WHO website).

Last, there is a need to further study the effects of comorbidity with bipolar disorder and schizophrenia in people with other physical and mental illnesses, as the preliminary analysis

in this thesis and other research has shown that it may be an important contributor to mortality. However as mentioned earlier, a number of important unresolved questions remain, including how to define comorbidity SMI validly and reliably using routinely collected records, whether the pathophysiological mechanisms underlying mortality in people with comorbid SMI are the same as people with SMI as a main diagnosis, and whether the recent epidemiology of comorbid SMI mirrors the epidemiology of SMI as a main diagnosis in England.

Clinical and policy implications

These results have particular clinical and policy relevance in the context of the implementation of the new national mental health strategy in England which states that 'more people with mental health problems will have good physical health' as one of its objectives, specifically stating the objective that 'fewer people with mental health problems will die prematurely' (2010).

The results from this thesis strongly point to the need for continued action to target risk factors particularly to lower the risk for these people in the first year following discharge from hospital (Goldacre, Seagroatt et al. 1993) for both natural and unnatural causes of death, including known risk factors for circulatory and respiratory disease the main causes of natural deaths seen in this thesis which have been increasing in populations with bipolar disorder and schizophrenia over the last decade.

The findings indicate that current medical and public health technologies to tackle avoidable causes of mortality could have a large effect in reducing the mortality gap, at least in the first year after discharge, and have an impact on the gender inequalities in mortality. Thus a logical policy approach would be ensure that people with bipolar disorder and schizophrenia have the access to the best possible medical and public health interventions (2009). This would include promoting good access to general medical, including primary care for people

with SMI and concurrent physical health problems to allow early detection, treatment and good follow-up care.

Secondly, it would involve providing better access to public health and healthy living services for people with SMI, helping them to make healthy lifestyle choices, including encouraging people with SMI to stop smoking, reduce their alcohol intake, eat healthily and increase the amount of physical exercise they undertake to reduce the risk factors for premature deaths.

Challenge for primary care

Given that the majority of psychiatric and general medical management of people with SMI is undertaken outside of the hospital setting, a reduction of the mortality gap would require a substantial amount of input from General Practitioners (GPs), Community Psychiatric Nurses (CPNs), district nurses, practice nurses and other community nurses. This recommendation must also be viewed in the context of the forthcoming reorganisation of the National Health Service in England, including the lead role taken by GP commissioning, and the focus on an outcomes-driven National Health Service (2010).

As mentioned earlier good clinical management of bipolar disorder and schizophrenia revolves around early diagnosis, the prompt treatment of acute psychiatric episodes, re-integration into the community, and the prevention of further acute psychiatric events and complications including physical ill-health (Katona and Robertson 2000; Belmaker 2004; Picchioni and Murray 2007; Gelder, Andreasen et al. 2009; Van Os and Kapur 2009).

Effective primary care services are essential for these functions and for tackling the underlying reasons for physical illness and mortality in these populations, such as high levels of smoking, substance abuse, unhealthy diets and physical inactivity.

Well trained and observant primary care practitioners could help spot and minimise the impact from the metabolic side effects of anti-psychotic medications (De Hert, Schreurs et al. 2009).

Well engaged social workers, CPNs and community advocates including elected officials could help address the issue of stigma and discrimination for people with severe mental illness and tackle difficulties with accessing appropriate medical and psychiatric treatments, including preventative health measures (Lawrence and Kisely 2010).

Challenge for secondary care

In a recent editorial Brian Millar suggested that inpatient psychiatric hospital admission can provide a critical window to identify patients at risk of physical illness and ensure that they are offered appropriate physical health care during admission and follow-up after discharge (Miller 2011). This requires better education of psychiatrists on risk factors for physical illness, better integration and communication between mental and physical healthcare services; and primary and secondary care (2009). This includes ensuring optimal management of anti-psychotic medications for people with SMI (2009).

Challenge for public health

Apart from the need to engage people with SMI in current public health and health promotion interventions, including programmes aimed at reducing deliberate self-harm and suicide (1999; 2002; 2002), smoking (2008; 2008; 2009; Banham and Gilbody 2010; Tsoi, Porwal et al. 2010; 2011), alcoholism, and drug misuse (2007; 2007), and other lifestyles associated with increased mortality (2004; 2011), there is the need for specific research into physical illness in those with SMI, especially methods for early detection of life-threatening illness, and health promotion interventions that work in the most vulnerable, high-risk populations.

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RESEARCH

Mortality after hospital discharge for people with schizophrenia or bipolar disorder: retrospective study of linked English hospital episode statistics, 1999-2006

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Abstract

Objective To investigate whether the mortality gap has reduced in recent years between people with schizophrenia or bipolar disorder and the general population.

Design Record linkage study.

Setting English hospital episode statistics and death registration data for patients discharged 1999-2006.

Participants People discharged from inpatient care with a diagnosis of schizophrenia or bipolar disorder, followed for a year after discharge.

Main outcome measures Age standardised mortality ratios at each time, comparing the mortality in people with schizophrenia or bipolar disorder with mortality in the general population. Poisson test of trend was used to investigate trend in ratios over time.

Results By 2006 standardised mortality ratios in the psychiatric cohorts were about double the population average. The mortality gap widened over time. For people discharged with schizophrenia, the ratio was 1.6 (95% confidence interval 1.5 to 1.8) in 1999 and 2.2 (2.0 to 2.4) in 2006 (P<0.001 for trend). For bipolar disorder, the ratios were 1.3 (1.1 to 1.6) in 1999 and 1.9 (1.6 to 2.2) in 2006 (P=0.06 for trend). Ratios were higher for unnatural than for natural causes. About three quarters of all deaths, however, were certified as natural, and increases in ratios for natural causes, especially circulatory disease and respiratory diseases, were the main components of the increase in all cause mortality.

Conclusions The total burden of premature deaths from natural causes in people with schizophrenia or bipolar disorder is substantial. There is a need for better understanding of the reasons for the persistent and increasing gap in mortality between discharged psychiatric patients and the general population, and for continued action to target risk factors for both natural and unnatural causes of death in people with serious mental illness.

Introduction

Schizophrenia has been described as a life shortening condition,[1] and many studies have shown that people with schizophrenia or bipolar disorder have higher mortality rates than the general population, both as a result of natural[2-10] and unnatural causes,[2-6] including suicide. Over the past decade several strategies have been implemented in England and Wales aimed at reducing the mortality gap between people with serious mental illness and the general population, including those to address deliberate self harm and to reduce suicide,[7-9] to decrease smoking,[10-12] alcoholism, and drug misuse,[13 14] and to deal with other lifestyles associated with increased mortality.[15 16] Recent studies have suggested that the rate of suicide has been stabilising among people with mental disorders as a whole[17-21]; however, trends in mortality for people with schizophrenia or bipolar disorder remain poorly characterised, particularly the relative contributions of natural and unnatural causes. The United Kingdom government's recent mental health strategy states that "more people with mental health problems will have good physical health" as one of its objectives, specifically stating that "fewer people with mental health problems will die prematurely."[22] It is therefore timely to review the level of and trends in these recognised inequalities.

We investigated trends in mortality between 1999 and 2006 during the year after discharge from hospital for people with schizophrenia or bipolar disorder as the principal diagnosis at discharge. We compared mortality in these populations with mortality in the general population of equivalent age in England to determine whether the "mortality gap" between people with these mental disorders and the general population has narrowed in recent years and to describe the relative contributions from natural and unnatural causes of death.

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Method

Data sources and population included in this study

Our data for analysis came from a linked dataset of English national hospital episode statistics and data from death certification built by the team that developed and manages the Oxford record linkage study. The hospital episode statistics component of the dataset includes statistical abstracts of records of all inpatient episodes undertaken in National Health Service (NHS) trusts in England, including acute hospitals and mental health trusts. Information about deaths came from death certificates held by the Office for National Statistics. This information included the date of death and the causes of death, which were coded by the Office for National Statistics using the ninth and 10th revisions of the international classification of diseases (ICD-9 and ICD-10).

We extracted all records of discharges from inpatient care in England from 1 January 1999 to 31 December 2006 with either schizophrenia (ICD-10 codes F20-29) or bipolar affective disorder (ICD-10 code F31) as the principal diagnosis on the discharge record.

Our primary outcome was mortality within 365 days after psychiatric inpatient care as defined above. We also investigated deaths from unnatural and natural causes. Unnatural deaths were defined on the basis of ICD-10 codes V01-Y98 or ICD-9 codes E800-999 recorded anywhere on the death certificate; the remaining deaths were classified as natural. To allow more detailed interpretation of deaths under these broad categories we have also presented data for deaths from the following specific causes where there were sufficient deaths to provide a stable estimate of risk of mortality—namely, deaths from cardiovascular disease (ICD-10 codes I00-99, ICD-9 codes 390-459), respiratory disease (ICD-10 codes J00-99, ICD-9 codes 460-519), cancer (ICD-10 codes C00-D48, ICD-9 codes 140-239), accidents (ICD-10 codes V01-X59, ICD-9 codes E800-929), and suicide/deaths from undetermined intent (ICD-10 codes X60-89 and Y10-34, ICD-9 codes E950-959 and E980-989).

Analysis

We calculated mortality after hospital discharge as age and sex standardised mortality ratios, comparing mortality in people with schizophrenia or bipolar disorder with mortality in the general population of England. Standardisation was done by using the indirect method, in five year age groups, with the age and sex specific mortality rates of England in the same time periods as the standard. These age and sex specific rates were applied to the age and sex structure of each of the discharge cohorts with schizophrenia or bipolar disorder to calculate an "expected" number of deaths. The observed number was compared with the expected number to calculate the standardised mortality ratios. Its confidence intervals were calculated as described elsewhere.[23] We further compared the mortality rates in three broad age groups: <45, 45-64, and 65-84 (with age standardisation, as above, using five year age groups within each truncated broader age group). We excluded analysis of those aged over 85 because of small numbers.

We used the Poisson test of trend to investigate whether there was a significant trend in standardised mortality ratios over time.[24]

Results

Trends in discharges with schizophrenia and bipolar disorder

For this study we included 100 851 discharges from hospital for bipolar disorder and 272 248 discharges for schizophrenia in England for 1999-2006. Tables 1⇓ and 2⇓ show the basic demographic characteristics of the populations. Over the course of the study, the total number of discharges for bipolar disorder decreased by 3.9% from 12 369 to 11 888 (table 1) and the total number of discharges for schizophrenia decreased by 10.9% from 35 348 to 31 486 (table 2). About three in four of the deaths in each of the two cohorts were from natural causes.

Standardised mortality ratios for schizophrenia and bipolar disorder

Age and sex standardised mortality ratios in the psychiatric cohorts were about double the population average. For example, in the 2006 cohort the ratio was 2.2 in the population discharged with schizophrenia and 1.9 in the population discharged with bipolar disorder. Standardised mortality ratios were higher in younger than in older people: in those aged under 45 discharged in 2006, the ratios were 6.2 (95% confidence interval 4.9 to 7.5) for schizophrenia and 3.4 (1.7 to 5.1) for bipolar disorder compared with 2.0 (1.7 to 2.3) and 1.8 (1.4 to 2.2), respectively, in people aged 65-84 (tables 3⇓ and 4⇓). Men with a discharge diagnosis of schizophrenia had a significantly higher risk of death within the first year than women. For example, in the 2006 cohort the standardised mortality ratio for men was 3.2 (2.8 to 3.6) and 1.8 (1.5 to 2.1) for women (table 4⇓). There was no significant sex difference in mortality risk for those discharged with a diagnosis of bipolar disorder (table 3⇓).

Trends in mortality ratios

As shown in table 4⇓ and figure 1⇓, standardised mortality ratios for people with schizophrenia increased from 1.6 (1.5 to 1.8) in people discharged in 1999 to 2.2 (2.0 to 2.4) in people discharged in 2006. The Poisson test for trend confirmed that the trend in risk of mortality was significant (P<0.001). For people with bipolar disorder, standardised mortality ratios increased from 1.3 (1.1 to 1.6) in people discharged in 1999 to 1.9 (1.6 to 2.2) in people discharged in 2006 (table 3⇓). The Poisson test of trend had results of borderline significance (P=0.06). Figures 2 and 3⇓⇓ summarise the data for the people with bipolar disorder or schizophrenia and the general population expressed as rates (to give absolute values). While the mortality rates in the general population tended to decline over time, those in the populations with mental disorders did not. Compared with the mortality rate for the general population, the mortality gap remained fairly stable for adults aged under 65; for those aged 65-84, however, the mortality gap widened during the study period.

Standardised mortality ratios for unnatural/natural causes and specific causes

For unnatural causes, the standardised mortality ratios showed no evidence of a narrowing mortality gap. In people with schizophrenia they were 11.6 (9.5 to 13.7) in the 1999 cohort and 11.6 (9.3 to 13.9) in the 2006 cohort. The corresponding figures for bipolar disorder were 9.3 (6.0 to 12.7) and 12.6 (8.6 to 16.6). Numbers in individual age groups were small, but there was no evidence of a narrowing of the gap in any age group (table 5⇓).

For natural causes, the mortality gap widened (table 6⇓). For people with schizophrenia, the standardised mortality ratio was 1.2 (1.1 to 1.4) in the 1999 cohort and 1.7 (1.5 to 1.9) in the 2006 cohort. The corresponding figures for bipolar disorder were 1.1 (0.9 to 1.3) and 1.4 (1.2 to 1.7). Table 7⇓ shows that deaths from cardiovascular disease and respiratory diseases accounted for most of this increase. From 1999 to 2006, in those with schizophrenia, the standardised mortality ratios for circulatory disease rose from 1.6 (1.4 to 1.9) to 2.5 (2.1 to 2.9), while the risk of death from respiratory disease increased from 3.1 (2.6 to 3.6) to 4.7 (3.8 to 5.6). The figures for those discharged with bipolar disorder rose from 1.6 (1.2 to 2.0) to 2.5 (1.9 to 3.1) for circulatory disease and from 3.0 (2.1 to 3.8) to 5.8 (4.3 to 7.3) for respiratory disease.

Discussion

Principal findings

The risk of death for people recently discharged from inpatient psychiatric care in England is significantly higher than that in the general population. This excess risk was observed for patients with a diagnosis of schizophrenia and for those with a diagnosis of bipolar disorder. Our findings of a persistent mortality gap in England in patients discharged between 1999 and 2006 are similar to results recently published by Tiihonen et al on all cause mortality in people with schizophrenia over a similar time period in Finland.[25 26] Additionally, our findings suggest that the differential mortality for people with schizophrenia has widened in some groups, a result that is similar to the findings from a systematic review by Saha et al in 2007.[27] Much of the increase in mortality is attributable to deaths from natural causes, especially circulatory disease and respiratory disease. Our findings support the recommendation of Saha et al that "in light of the potential for second-generation antipsychotic medications to further adversely influence mortality rates . . . optimizing the general health of people with schizophrenia warrants urgent attention."[27]

Strengths and weaknesses

Strengths of this study include its large size and the fact that it includes all records of discharges with a diagnosis of schizophrenia or bipolar disorder in the study period and is therefore nationally representative. By linkage to national mortality data we have included comprehensive information on mortality in these vulnerable groups, especially in the period after discharge from hospital when the risk of death is greatest.[2] In addition, to the best of our knowledge, ours are the first published findings on trends in mortality over the past decade for people with bipolar disorder in England, a condition that shares some clinical and management characteristics with schizophrenia.[28] These study characteristics aid the generalisability of our findings compared with previous studies in the UK, which have been limited to case registers within individual mental health trusts.[29 30]

To quantify the mortality gap and assess the trend in risk of mortality for people with schizophrenia or bipolar disorder, we calculated standardised mortality ratios, which take into account differences in the age structure of the cases, as well as changes in the underlying mortality rates of the general population. The widening gap in standardised mortality ratios alone could represent an absolute rise in mortality in the psychiatric population or a fall in mortality in the general population in conjunction with a smaller fall in mortality in the psychiatric population. Accordingly, we have presented rates for all causes of death after discharge compared with national mortality rates over the same period, which allowed us to compare trends in the absolute difference in mortality risk between the groups. Both figures—the standardised mortality ratios and the rates—show that the risk of mortality after discharge is substantial and that the gap in risk, whether calculated in relative or absolute terms, remains substantial. The standardised mortality ratios for schizophrenia and bipolar disorder towards the end of this observation period are similar to those recently reported from the South London and Maudsley Biomedical Research Centre psychiatric case register for 2007-9, which also found a similarly pronounced excess in younger patients.[29]

Potential limitations include the usual caveats concerning the use of routinely collected data, including information from hospital records and death certificates, which are not collected for research purposes.[31-34] There are also caveats about the validity of a dichotomy between "natural" and "unnatural" categories of death, although the definitions of these categories from the ICD codes were standard.[35 36] The case groups consisted of people who had been recently admitted to hospital with a principal diagnosis of a mental disorder during the period in question and cannot be said to represent all people with the disorders; they are likely to represent a more severely affected group at a period of higher risk. The severity of the disorders in the case groups might have changed over the monitoring period because of changes in admission policy. Keown et al found little evidence of any significant decrease in admissions for schizophrenia or bipolar disorder during this period,[37] and our finding of minor reductions in discharges over the observation period compared with the increases in standardised mortality ratios suggests that the concentration of mortality risk in these patients admitted to hospital is unlikely to be the sole explanation for the widening mortality gap, although residual confounding with severity of illness cannot be excluded entirely.

Interpretation, unanswered questions, and need for further work

Schizophrenia and bipolar disorder are known to be associated with a higher risk of mortality.[1] Over the past decade the contribution of natural causes to excess mortality in people with severe mental illness has been increasingly recognised, particularly the impact of coronary heart disease, stroke, and cancer.[38] For example, Osborn and colleagues used information from the UK General Practice Research Database to follow up a community sample of people with severe mental illness and found that these people had a significantly increased risk of death from coronary heart disease and stroke compared with controls that was not wholly explained by antipsychotic medication, smoking, or social deprivation.[39]

While knowledge about the specific causes of death in severe mental illness are becoming clearer, the pathogenic mechanisms that culminate in higher than expected mortality from natural causes in people with mental disorder are little understood and likely to be complex.[40 41] Mechanisms acting through the direct effects of symptoms of mental disorder are unlikely to have a large effect on mortality from natural causes, although they are likely to influence death from suicide and other unnatural causes.[42] Premature deaths from natural causes are likely to be influenced by adverse lifestyle and social factors associated with the presence of mental illness—such as smoking, use of alcohol and illicit drugs, and exposure to poor housing and social conditions[40 43]—or the adverse effects of antipsychotic medication.[44 45] It has been suggested, however, that these factors do not account for all the excess mortality,[39] and there is an urgent need for more research to understand the contribution of the six leading global risk factors for mortality identified by

WHO—namely, hypertension, smoking, raised glucose concentration, physical inactivity, overweight and obesity, and high cholesterol concentration—to excess mortality in people with severe mental illness, including schizophrenia and bipolar disorder.[41]

Our results reinforce the need for further research in the UK as the mortality gap has not decreased and is increasing in some groups, such as those aged over 65. These results have particular policy relevance in the context of the implementation of the new national mental health strategy in England. They strongly point to the need for continued action to target risk factors for both natural and unnatural causes of death, including known risk factors for circulatory and respiratory disease, particularly to lower the risk for these people in the year after discharge from hospital. It is encouraging that the government has recognised and prioritised the importance of preventing premature mortality in its recently published mental health strategy.[22] A reduction of the gap is also a challenge for the forthcoming reorganisation of the NHS in England, for general practitioner commissioning, and for the reorganisation's emphasis on an NHS driven by outcomes. The already widening mortality gap between people with schizophrenia or bipolar disorder and the general population, however, suggests that these policies might be challenging aspirations.

Contributors: UH and MG were responsible for the conception and design of this study. UH analysed the data. All authors were involved in the interpretation of data, drafting the article, and approval of the final manuscript. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. UH is guarantor.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The current work programme of analysis using the linked datasets held at the unit of health-care epidemiology was approved by an ethics committee of the NHS central office for research (reference No 04/Q2006/176).

Data sharing: Hospital Episodes Statistics and mortality data can be obtained through the NHS Information Centre and the Office for National Statistics, respectively. More detailed aggregated statistical tables than those shown in this paper are available from the corresponding author.

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What is already known on this topic

People with schizophrenia or bipolar disorder have higher mortality rates than the general population, both as a result of natural and unnatural causes

Recent evidence suggests that the rate of suicide and death from unnatural causes has been stabilising among people with mental illness in the UK

The English government's recent mental health strategy has stated clearly that "fewer people with mental health problems will die prematurely"

What this study adds

The mortality gap between people with schizophrenia or bipolar disorder who have been recently discharged from hospital and the general population persisted between 1999 and 2006 in England

For some age groups, such as those aged 65-84, the mortality gap has increased

Most of this excess mortality was the result of deaths from natural causes, especially deaths from circulatory and respiratory diseases

Tables

Table 1| Characteristics of people discharged with principal diagnosis of bipolar disorder (ICD-10 code F31) in England, 1999-2006

					Deaths within 365 days	
Year of discharge	No of discharges	No of people discharged	% male	Median age (men/women)	From all causes	From unnatural causes (% of all deaths)
1999	12 369	9312	38	42/48	132	30 (22.7)
2000	12 285	9217	38	42/48	132	35 (26.5)
2001	12 803	9384	38	43/48	143	40 (27.9)
2002	13 153	9612	39	43/48	161	38 (23.6)
2003	12 757	9723	39	44/48	175	46 (26.3)
2004	13 221	10 102	40	43/48	158	51 (32.3)
2005	12 375	9284	39	44/48	156	43 (27.6)
2006	11 888	9086	41	44/48	148	38 (25.7)

Table 2| Characteristics of people discharged with principal diagnosis of schizophrenia (ICD-10, codes F20-29) in England, 1999-2006

					Deaths within 365 days	
Year of discharge	No of discharges	No of people discharged	% male	Median age (male/female)	From all causes	From unnatural causes (% of all deaths)
1999	35 348	27 133	58	34/44	416	114 (27.4)
2000	33 793	25 785	58	34/44	427	113 (26.5)
2001	34 478	25 870	59	35/44	408	111 (27.2)
2002	34 105	25 524	60	35/44	389	86 (22.1)
2003	33 665	25 856	60	35/44	459	106 (23.1)
2004	35 540	27 425	60	35/44	429	123 (28.7)
2005	33 833	25 709	60	36/44	414	112 (27.1)
2006	31 486	24 205	61	36/44	376	96 (25.5)

Table 3| **Age and sex standardised all cause mortality ratios in year after hospital discharge between 1999 and 2006 with principal diagnosis of bipolar disorder (ICD-, 10, code F31) by age**

Year of discharge	All ages	<45 years	45-64 years	65-84 years
Men and women				
1999	1.3	4.0	1.7	1.1
2000	1.4	3.9	2.3	1.3
2001	1.5	5.2	2.2	1.3
2002	1.7	4.6	2.7	1.6
2003	1.8	5.4	2.6	1.6
2004	1.8	8.0	2.7	1.4
2005	1.8	4.4	2.6	1.7
2006	1.9	3.4	2.6	1.8
Men				
1999	1.7	5.8	1.8	1.3
2000	1.8	3.7	2.1	1.6
2001	1.9	5.1	2.6	1.5
2002	2.1	6.3	2.5	1.6
2003	2.1	5.1	2.9	1.6
2004	2.3	8.6	2.6	1.7
2005	2.0	4.7	2.4	1.9
2006	2.3	5.1	2.3	2.0
Women				
1999	1.4	2.3	2.0	1.2
2000	1.5	4.8	2.9	1.2
2001	1.6	5.3	2.1	1.4
2002	1.8	2.8	3.2	1.8
2003	1.9	6.1	2.6	1.8
2004	1.6	7.9	3.0	1.3
2005	1.9	4.4	3.0	1.7
2006	1.8	1.5	3.1	1.9

Table 4| **Age and sex standardised all cause mortality ratios in year after hospital discharge between 1999 and 2006 with principal diagnosis of schizophrenia (ICD-10, codes F20-29) by age**

Year of discharge	All ages	<45 years	45-64 years	65-84 years
Men and women				
1999	1.6	6.9	3.4	1.3
2000	1.9	7.5	3.5	1.7
2001	1.7	6.5	3.4	1.7
2002	1.8	6.2	3.3	1.6
2003	2.2	6.7	4.3	2.0
2004	2.1	7.5	3.6	1.8
2005	2.3	9.1	3.5	1.9
2006	2.2	6.2	3.9	2.0
Men				
1999	2.3	6.1	3.0	1.3
2000	2.6	6.8	3.2	1.8
2001	2.5	5.8	3.4	1.6
2002	2.5	5.5	3.5	1.6
2003	2.9	6.2	4.2	2.0
2004	3.0	6.48	4.1	2.0
2005	3.3	8.7	3.2	2.3
2006	3.2	6.1	4.0	2.2
Women				
1999	1.6	7.3	4.2	1.4
2000	1.9	8.2	4.2	1.8
2001	1.7	6.4	3.5	1.9
2002	1.7	6.1	3.0	1.7
2003	2.0	5.8	4.4	2.1
2004	1.8	7.9	2.9	1.8
2005	1.9	6.6	3.9	1.7
2006	1.8	4.1	3.6	2.1

Table 5| **Age and sex standardised mortality ratios for unnatural causes of death in year after hospital discharge between 1999 and 2006 by age and principal diagnosis**

Year of discharge	All ages	<45 years	45-64 years	65-84 years
Bipolar disorder (ICD-10, code F31)				
1999	9.3	10.6	10.6	6.5
2000	11.0	9.4	17.6	9.5
2001	12.3	14.1	18.7	6.6
2002	11.9	11.2	21.2	4.2
2003	13.9	17.2	13.0	15.1
2004	15.6	22.3	18.9	7.1
2005	14.2	11.5	27.5	7.5
2006	12.6	13.8	15.4	10.5
Schizophrenia (ICD-10, codes F20-29)				
1999	11.6	15.2	16.0	3.9
2000	12.3	16.7	12.2	8.7
2001	11.6	15.0	16.6	7.3
2002	9.8	13.0	10.0	7.9
2003	11.9	14.8	15.2	9.9
2004	13.6	17.9	18.1	4.8
2005	13.8	19.3	13.1	8.2
2006	11.6	15.2	14.3	6.5

Table 6| **Age and sex standardised mortality ratios for natural causes of death in year after hospital discharge between 1999 and 2006 by age and principal diagnosis**

Year of discharge	All ages	<45 years	45-64 years	65-84 years
Bipolar disorder (ICD-10, code F31)				
1999	1.1	1.0	1.3	1.1
2000	1.1	1.4	1.5	1.1
2001	1.1	1.3	1.3	1.2
2002	1.4	2.0	1.7	1.5
2003	1.4	0.7	2.0	1.4
2004	1.2	2.3	1.8	1.3
2005	1.4	1.8	1.2	1.6
2006	1.4	0.3	1.8	1.6
Schizophrenia (ICD-10, codes F20-29)				
1999	1.2	2.3	2.7	1.3
2000	1.5	2.6	3.0	1.6
2001	1.3	2.2	2.7	1.6
2002	1.5	2.9	2.9	1.5
2003	1.8	2.9	3.7	1.8
2004	1.6	2.7	2.8	1.7
2005	1.8	4.6	2.9	1.8
2006	1.7	2.7	3.2	1.8

Table 7| **Age and sex standardised mortality ratios for death in year after hospital discharge between 1999 and 2006 by principal psychiatric diagnosis and specific cause of death**

Year of discharge	Circulatory disease*	Cancer†	Respiratory disease‡	Accidents§	Suicide and undetermined intent¶
Bipolar disorder (ICD-10, code F31)					
1999	1.6	0.4	3.0	6.8	13.5
2000	1.4	0.7	2.5	5.2	21.2
2001	1.6	0.5	3.7	4.7	24.8
2002	1.8	0.8	5.7	4.9	20.2
2003	1.8	0.9	5.0	4.0	27.7
2004	1.8	0.5	4.9	4.8	32.1
2005	2.1	0.6	4.6	5.0	29.5
2006	2.5	0.6	5.8	6.6	19.8
Schizophrenia (ICD-10, codes F20-29)					
1999	1.6	0.8	3.1	6.5	19.5
2000	2.0	1.0	3.5	7.5	19.6
2001	1.6	0.9	4.0	5.8	21.8
2002	1.9	1.0	4.4	4.2	17.8
2003	2.5	1.1	5.3	5.3	23.3
2004	2.2	1.1	5.6	6.8	24.7
2005	2.4	1.1	6.0	8.3	24.0
2006	2.5	1.3	4.7	6.3	20.9

*ICD-10: I00-I99; ICD-9: 390-459.
†ICD-10: C00-D48; ICD-9: 140-239.
‡ICD-10: J00-99; ICD-9: 460-519.
§ICD-10: V01-X59; ICD9: E800-E929.
¶ICD-10: X60-X84, Y10-Y34; ICD-9: E950-E959, E980-E989.

Figures

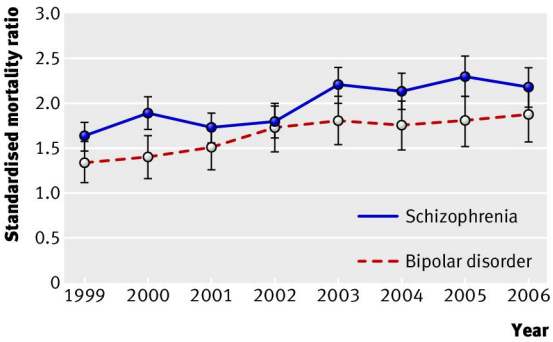

Fig 1 Trend in standardised 365 day all cause mortality ratio for all people discharged from hospital with principal diagnosis of bipolar disorder or schizophrenia

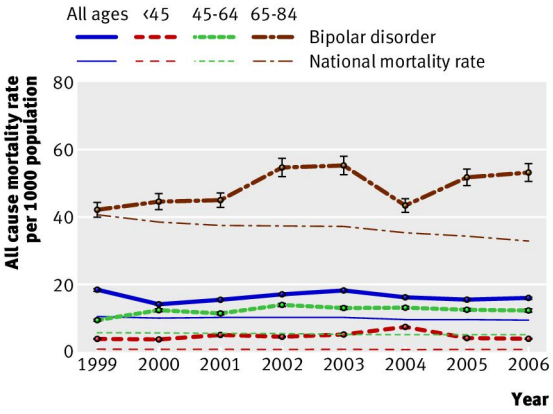

Fig 2 All cause mortality rate within 365 days after discharge per 1000 people discharged with principal diagnosis of bipolar disorder by age

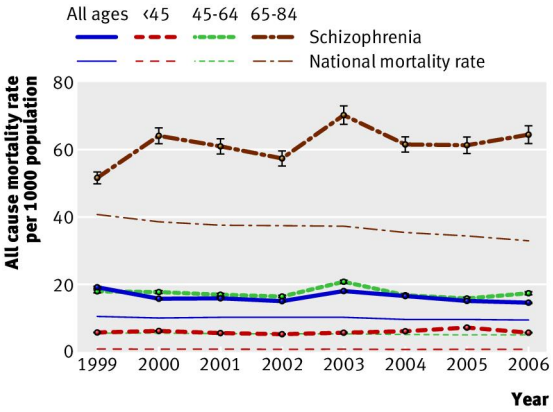

Fig 3 All cause mortality rate within 365 days after discharge per 1000 people discharged with principal diagnosis of schizophrenia by age

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Avoidable mortality in people with schizophrenia or bipolar disorder in England

Hoang U, Goldacre MJ, Stewart R. Avoidable mortality in people with schizophrenia or bipolar disorder in England.

Objective: To quantify the extent of 'avoidable mortality' in those with schizophrenia or bipolar disorder and to quantify the effect a reduction in these might have on the mortality gap associated with severe mental illness.
Method: A cohort was studied of people aged <75 years, discharged from inpatient care with schizophrenia or bipolar disorder in 2006–2007, and followed up for 365 days. Standardised mortality ratios (SMRs) were calculated followed by hypothetical SMRs, estimating the residual mortality gap if 'avoidable' causes and suicide in the cohorts had occurred at the same level as those in the general population.
Results: Avoidable deaths comprised 60.2% and 59.2% of all deaths in the schizophrenia and bipolar disorder cohorts respectively. All-cause SMRs were 4.23 (95% CI 3.85–4.60) and 2.60 (2.21–3.00) respectively. After discounting the excess attributable to avoidable causes and suicide, the SMRs fell to 2.38 (2.09–2.66) and 1.66 (1.35–1.98) respectively.
Conclusion: Bringing mortality from avoidable causes and suicide down to general population levels would reduce the overall mortality excess in severe mental illness substantially, by about 50%, but would not eliminate it. Other underlying factors beyond those conventionally considered as 'avoidable' need further research.

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Key words: schizophrenia; bipolar disorder; mortality

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Significant outcomes

- There is a substantial 'mortality gap' between mortality rates in people with severe mental illness and the general population.
- If deaths from 'avoidable causes' in people with schizophrenia or bipolar disease came down to the level of deaths from avoidable causes in the general population, the mortality gap would reduce by about 50% but would not be eliminated.
- We recommend that more research needs to be undertaken to characterise 'non-avoidable causes' of death in these populations to allow practical insights into ways of increasing life expectancy.

Limitations

- A weakness of our study is the reliance on hospital records to define our study cohort. People who have been recently hospitalised for psychiatric care are known to have higher mortality rates than other people with psychiatric disorders, and so our results may not be applicable to people with schizophrenia and bipolar disorder who are not hospitalised.
- Our study is restricted to follow-up over the first 365 days following discharge, which will have underestimated the true impact of avoidable deaths over the patients' lifespan.
- Our study relied on routinely collected data to define our cohorts and outcomes, which are not primarily collected for research purposes, and we do not have information on the underlying criteria used to define the psychiatric illnesses or the causes of death.

Introduction

People with severe mental illness (SMI) are known to have higher mortality rates than other people within the general population (1, 2). Recent evidence suggests that this 'mortality gap' has widened over the past decade in England and several other countries, especially for people with schizophrenia and bipolar disorder, and serves as a call to action for everyone involved in the care of people with severe mental illness (3–6).

Mortality rates for unnatural causes of death, including suicide, are high in people with SMI, but these are uncommon and much of the excess mortality associated with SMI is from natural causes (2, 7). Whilst there is a consensus that the underlying mechanisms resulting in mortality amongst this group are likely to be complex (2), there is little quantitative evidence concerning how much of the excess mortality could be avoided either through the provision of better medical and psychiatric care or from the provision of better preventative services for those with SMI. The concept of 'avoidable mortality' originally introduced by Rutstein et al. and recently updated by other authors offers a method to quantify the proportions of these deaths in a population (8–11).

Aims of the study

In this study, we sought to quantify the level of 'avoidable' deaths in a cohort of people with schizophrenia or bipolar disorder in England in the first year following hospital discharge, often recognised as the period of highest risk for death. To the best of our knowledge, ours is the first study to present avoidable mortality risk in people with bipolar disorder.

We specifically sought to answer the question whether the mortality excess in people with schizophrenia and bipolar disorder would be reduced or eliminated if deaths in these patients from causes that should be preventable and/or amenable to treatment were reduced to their levels in the general population'.

Material and methods

Population and data set

A linked data set containing data from English national Hospital Episode Statistics (HES, data supplied by the NHS Information Centre) and death registrations (supplied by the Office for National Statistics), linked by the Oxford Record Linkage Group(12, 13), was analysed for this study. The hospital component of the data set includes records of all inpatient admissions, including day cases, in NHS acute and psychiatric hospitals in England. This information included the date of death and the causes of death which were coded, by the Office for National Statistics (ONS), using the International Classification of Diseases (ICD) revision 10.

We extracted all records of discharges from inpatient care for people less than 75 years on admission in England between 1 January 2006 and 31 December 2007 with either schizophrenia (ICD10 codes F20-F29), or bipolar disorder (ICD10 code F31) as the principal diagnosis on the discharge record. Follow-up for 365 days after discharge, all performed by record linkage within the data set, was to 31 December 2008.

Avoidable mortality

The primary outcome for this study was mortality in people with schizophrenia or bipolar disorder compared with the general population, subdividing their excess mortality into deaths from avoidable causes and other deaths. Avoidable causes of death were defined by a list of diagnostic codes (10, 14) which are shown, with age ranges where relevant, in the web appendix. Deaths that are considered 'avoidable' have been updated by the ONS from Rutstein's original definition in 1976 (8, 15). They include the following categories i) deaths which could be avoided through the efforts of healthcare services, termed 'amenable' (i.e. focusing on deaths arising potentially because of less than optimal healthcare provision); ii) deaths which could be avoided by broader interventions, for example, accident prevention, termed 'preventable' (deaths from suicide and undetermined intent were included in this group); iii) deaths which could be amenable through the efforts of healthcare services or could be prevented through broader interventions, termed 'avoidable' deaths (14). Some deaths classified as 'avoidable' are considered as both 'amenable' and 'preventable'; thus, the number of 'avoidable' deaths is not equivalent to the sum of 'amenable' and 'preventable' deaths.

In this study, deaths from suicide and undetermined intent (ICD10 codes-X60 to X84, Y10 to Y34) were considered avoidable if they were recorded anywhere on the death certificate; deaths from the other diagnostic codes shown in the web appendix were included if they were the coded underlying cause of death. Deaths that were not classified as 'avoidable', as determined by their cause, were termed 'unavoidable'.

Analysis

The standard definition of avoidable causes of death takes an upper age threshold of 74 years as the maximum age at which deaths are assumed to be avoidable (10, 14). Accordingly, we calculated the percentage of avoidable deaths in people <75 years with schizophrenia or bipolar disorder.

To analyse the possible effects of a reduction in avoidable deaths in these populations, we calculated a series of hypothetical standardised mortality ratios (SMRs): these were the SMRs that would have prevailed if avoidable deaths were reduced to their levels in the general population. A brief explanation of the calculations undertaken is given below and in Fig. 1. Comparable calculations have been undertaken to estimate the upper limits of human longevity (16).

First, we calculated mortality from all-causes after hospital discharge as age and sex standardised mortality ratios, comparing mortality in the people with schizophrenia or bipolar disorder, with mortality in the general population of England. Standardisation was performed using the conventional indirect method, in 5-year age groups, using the age- and sex-specific mortality rates of England in the same time periods as the standard. These age- and sex-specific rates were applied to the age and sex structure of each of the discharge cohorts with schizophrenia or bipolar disorder to calculate an 'expected' number of deaths. The observed number was compared with the expected number to calculate the standardised mortality ratios (4); 95% confidence intervals for the SMRs were calculated as described elsewhere (17).

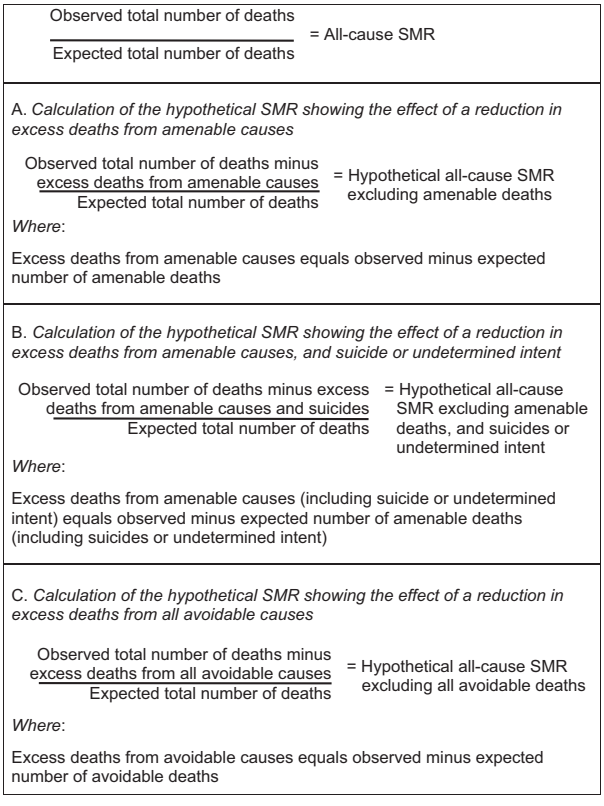

Fig. 1. Calculation of hypothetical SMRs starting from the actual all-cause SMR and showing the all-cause SMRs that would have prevailed if excess avoidable deaths were reduced.

Next, we calculated the number of excess amenable deaths by subtracting the observed number of amenable deaths from the expected number. All-cause SMRs were then re-calculated as above with the amenable component set to the level found in the general population. This first set of hypothetical SMRs shows what the all-cause SMR would have been if these cohorts had the same mortality risk from amenable causes as the general population and allows us to examine the effect of a reduction in amenable deaths.

As suicide and deaths from undetermined intent are an important contributor to excess deaths in those with severe mental illness (18), we calculated a second set of hypothetical SMRs, in the same way, by subtracting both excess amenable deaths and excess deaths from suicide or undetermined intent. This second set of hypothetical SMRs shows what the all-cause SMR would have been if the risk of death from amenable causes and suicide in these cohorts had been the same as the general population.

A final set of hypothetical SMRs were calculated by subtracting all excess avoidable causes of death. This last set of hypothetical SMRs shows what the all-cause SMR would have been if the risk of death in these cohorts from all avoidable causes had been the same as the general population. It allows us to examine the effect of a reduction in all avoidable deaths.

We repeated the analysis, calculating age-truncated SMRs, for people aged <65 years, <45 and <25 years (with age-sex standardisation, as above, using 5-year age groups within each truncated broader age group) to allows us to examine the differential effect of a reduction in avoidable deaths at different ages. We repeated the analysis for males and females separately, to examine the differential effect of a reduction in avoidable deaths for each sex separately.

Statistical analyses were performed with the SAS statistical software package (SAS version 9.3, 2011, Cary, NC).

Role of the funding source

The work of the authors is independent from the funders of this research. The views in this article

do not necessarily reflect those of the funding body. The funding body had no role in the analysis or interpretation of the data. The funding body had no role in the analysis or interpretation of the data. The authors had full access to the data in the study, were not paid by any external agency to write the study, and had final responsibility for the decision to submit for publication.

Results

Number of discharges for schizophrenia and bipolar disorder aged <75 years

There were 54 883 discharges for schizophrenia (for 37 607 individuals) and 20 690 discharges for bipolar disorder (for 14 017 individuals) in England between 1 January 2006 and 31 December 2007. Table 1 summarises demographic characteristics of the cohorts.

All-cause mortality and proportion of deaths from avoidable causes in people with schizophrenia and bipolar disorder

Within 365 days of discharge, there were 480 deaths amongst people recently discharged with schizophrenia, and 169 deaths in people recently discharged with bipolar disorder <75 years (Table 1). For people recently discharged with a principal diagnosis of schizophrenia, avoidable deaths comprised 60.2% of all deaths. Deaths potentially amenable to medical care accounted for 30.2% of deaths, whilst deaths from conditions that are potentially preventable through public health interventions accounted for 50.6% of all deaths (many causes on the list are regarded as both amenable and preventable). For people recently discharged with a principal diagnosis of bipolar disorder, avoidable deaths comprised 59.2% of all deaths. Amenable deaths accounted for 30.2%, whilst preventable deaths accounted for 49.1% of all deaths (see Table 1). 'Unavoidable' deaths, namely those deaths that remained after discounting 'avoidable' deaths, were distributed rather generally across major disease groups, without heavy concentration in any disease category (see Table 2).

Table 1. Number of discharges and number of people aged under 75 years, discharged with a principal diagnosis of schizophrenia or bipolar disorder, and their demographic characteristics, between 2006–2007, in England

	Principal diagnosis on discharge	
	Schizophrenia	Bipolar disorder
Number of discharges between 1st January 2006–31 December 2007	54 883	20 690
Number of people discharged between 1 January 2006–31 December 2007	37 607	14 017
% male	62	41
Deaths from all causes within 365 days of discharge	480	169
Number of deaths that are amenable** (% of all deaths)	145 (30.2%)	51 (30.2%)
Number of deaths that are preventable** (% of all deaths)	243 (50.6%)	83 (49.1%)
Number of deaths that are avoidable** (% of all deaths)	289 (60.2%)	100 (59.2%)

Consultation on definitions of avoidable mortality (UK ONS, 2011).
**Deaths from suicide and undetermined intent (ICD10 codes – X60 to X84, Y10 to Y34) were included in this group.
Note that many conditions classified as 'avoidable' are classified as both 'amenable' and 'preventable'; thus, the first two categories do not sum to the last (UK ONS, 2011).

Standardised mortality ratios

The all-cause SMRs for people with schizophrenia or bipolar disorder <75 years were, respectively, 4.23 (95% confidence interval.85–4.60) and 2.60 (2.21–3.00). Table 3 shows that equalising amenable deaths resulted in the SMR for people with schizophrenia falling from 4.23 to 3.34 (95% CI: 3.00–3.67). For those with bipolar disorder, the SMR was reduced from 2.60 to 2.19 (95% CI: 1.83 –2.55) in this way. Additionally, equalising suicide mortality gave a further reduction in the SMRs to 2.44 (95% CI: 2.15–2.73) for schizophrenia and to 1.70 (95% CI: 1.38–2.02) for bipolar disorder. Finally, equalising amenable deaths, suicides and all other preventable deaths did not eliminate the mortality gap, the SMR remaining at 2.38 (95% CI: 2.09–2.66) for schizophrenia and 1.66 (95% CI: 1.35–1.98) for bipolar disorder.

Table 3 also shows differences between men and women in the mortality gap with the general population. Sex-specific SMRs were higher in men than women; reducing deaths from avoidable causes had a marginally greater impact on men than

Table 2. Underlying causes of death within 365 days after discharge in people with a principal diagnosis of schizophrenia or bipolar disorder, and the percentage of deaths that were from unavoidable causes in each of four disease chapters

Underlying cause of death 365 days after discharge (ICD10 chapter headings and code ranges)	Number of unavoidable deaths in each chapter in people with: (% of all deaths in each chapter that were unavoidable)	
	Schizophrenia	Bipolar disorder
Neoplasms (ICD10 codes – C00-D48)	23 (47.9)	13 (61.9)
Diseases of the circulatory system (ICD10 codes – I00-I99)	49 (39.2)	13 (31.7)
Diseases of the respiratory system (ICD10 codes – J00-J99)	25 (29.1)	0 (0)
Diseases of the digestive system (ICD10 codes – K00-K93)	15 (88.2)	7 (87.5)

Table 3. Hypothetical SMRs for people aged under 75 years discharged with a principal diagnosis of schizophrenia or bipolar disorder, applying death rates from amenable causes, suicide and preventable causes at the levels in the general population, by sex

	SMR within 365 days after discharge	
Category	Schizophrenia	Bipolar disorder
Both sexes, aged under 75 years		
All-causes	4.23 (3.85–4.60)	2.60 (2.21–3.00)
All-causes minus excess amenable deaths*	3.34 (3.00–3.67)	2.19 (1.83–2.55)
All-causes minus excess amenable deaths* and suicides or deaths from undetermined intent	2.44 (2.15–2.73)	1.70 (1.38–2.02)
All-causes minus excess amenable deaths*, suicides or deaths from undetermined intent, and preventable deaths*	2.38 (2.09–2.66)	1.66 (1.35–1.98)
Males, aged under 75 years		
All-causes	4.55 (4.05–5.05)	2.66 (2.07–3.25)
All-causes minus excess amenable deaths*	3.54 (3.10–3.98)	2.34 (1.78–2.89)
All-causes minus excess amenable deaths* and suicides or deaths from undetermined intent	2.50 (2.13–2.87)	1.77 (1.29–2.25)
All-causes minus excess amenable deaths*, suicides or deaths from undetermined intent, and preventable deaths*	2.48 (2.11–2.85)	1.66 (1.20–2.13)
Females, aged under 75 years		
All-causes	3.68 (3.11–4.24)	2.88 (2.26–3.43)
All-causes minus excess amenable deaths*	2.98 (2.47–3.48)	2.29 (1.76–2.81)
All-causes minus excess amenable deaths* and suicides or deaths from undetermined intent	2.35 (1.90–2.80)	1.79 (1.33–2.25)
All-causes minus excess amenable deaths*, suicides or deaths from undetermined intent, and preventable deaths*	2.16 (1.73–2.59)	1.80 (1.34–2.27)

*Consultation on definitions of avoidable mortality (UK ONS, 2011).

women. For example, the SMR for men with schizophrenia decreased from 4.55 (95% CI: 4.05–5.05) to 2.48 (95% CI: 2.11–2.85) if avoidable causes of death were reduced, compared with a reduction from 3.68 (95% CI: 3.11–4.24) in women to 2.16 (95% CI: 1.73–2.59. There was no difference between men and women when reducing avoidable causes in people with bipolar disorder.

Further age-truncated analysis suggests that reducing avoidable deaths in people <45 years would have the greatest effect on reducing excess mortality. Table 4 shows that people with schizophrenia <45 years would experience a reduction of SMR from 7.13 (95% CI: 6.02–8.23) to 3.32 (95% CI: 2.57–4.07), whilst people with bipolar disorder <45 years would experience a reduction of SMR from 3.72 (95% CI: 2.32–5.13) to 1.59 (95% CI: 0.67–2.50) if avoidable causes of death were reduced to the same level as the general population.

Table 4. Hypothetical SMRs for people aged under 65, under 45 and under 25 discharged with a principal diagnosis of schizophrenia or bipolar disorder, applying death rates from amenable causes, suicide and preventable causes at the levels in the general population

	SMR within 365 days after discharge	
Category	Schizophrenia	Bipolar disorder
Both sexes, aged under 65 years		
All-causes	5.21 (4.67–5.75)	2.96 (2.39–3.54)
All-causes minus excess amenable deaths*	4.33 (3.84–4.82)	2.70 (2.15–3.25)
All-causes minus excess amenable deaths* and suicides or deaths from undetermined intent	2.89 (2.49–3.29)	1.85 (1.40–2.31)
All-causes minus excess amenable deaths*, suicides or deaths from undetermined intent, and preventable deaths*	2.77 (2.38–3.17)	1.81 (1.36–2.26)
Both sexes, aged under 45 years		
All-causes	7.13 (6.02–8.23)	3.72 (2.32–5.13)
All-causes minus excess amenable deaths*	6.71 (5.64–7.78)	3.58 (2.20–4.95)
All-causes minus excess amenable deaths* and suicides or deaths from undetermined intent	3.48 (2.71–4.26)	1.71 (0.76–2.66)
All-causes minus excess amenable deaths*, suicides or deaths from undetermined intent, and preventable deaths*	3.32 (2.57–4.07)	1.59 (0.67–2.50)
Both sexes, aged under 25 years		
All-causes	5.29 (3.17–7.41)	1.89 (0–4.02)
All-causes minus excess amenable deaths*	4.90 (2.87–6.94)	1.89 (0–4.02)
All-causes minus excess amenable deaths* and suicides or deaths from undetermined intent	2.47 (1.02–3.97)	1.41 (0–3.26)
All-causes minus excess amenable deaths*, suicides or deaths from undetermined intent, and preventable deaths*	2.18 (0.82–3.54)	1.32 (0–3.11)

*Consultation on definitions of avoidable mortality (UK ONS, 2011).

Discussion

There is a substantial excess mortality risk in people with schizophrenia and bipolar disorder <75 years, which is slightly greater for schizophrenia than for bipolar disorder. Almost two-thirds of all deaths within the first 365 days after discharge from inpatient care are potentially avoidable as judged by standard definitions of avoidable causes of death. Our findings suggest that reductions in these avoidable causes, which include suicide, could reduce the mortality gap appreciably, especially in people <45 years. In people with schizophrenia, reducing avoidable causes of death may also slightly narrow the gender difference in mortality excess that has been described by previous researchers (19). However, our hypothetical SMRs also indicate that reducing excess deaths classified

as avoidable does not eliminate the mortality gap between these case groups and the general population. Even after discounting excess deaths from all avoidable causes, people with schizophrenia, in their first year after their discharge from hospital, were still twice as likely to die as the general population. For people with bipolar disorder, the mortality excess remained one and half times greater than the general population. For both conditions, the residual excess mortality was accounted for by unavoidable deaths across a broad range of disease groups.

Strengths and weaknesses of our study

The large size of this study, and the fact that it includes all records of discharges with a diagnosis of schizophrenia or bipolar disorder in the study period nationally, is the strength of our study. To the best of our knowledge, this study is the largest to date on avoidable causes of death in people with schizophrenia (20–22) and the only one to examine avoidable mortality risk in those with bipolar disorder (23), a condition which shares many clinical and management characteristics with schizophrenia (24). These study characteristics aid the generalizability of our findings. We also use the latest definitions of avoidable mortality which incorporate understanding and consensus on the impact of the latest medical and surgical interventions on causes of death (10). Finally, our presentation of hypothetical SMRs allows policy makers to quantify the current effects of avoidable causes of death and the possible impact of different interventions to reduce these.

A weakness of our study is the reliance on the accuracy of routinely collected data, which are not primarily collected for research purposes. Recent evidence from Burns and colleagues has shown that the consistent and accurate recording of diagnosis across a range of conditions, especially the primary diagnosis for which reimbursement is calculated, has improved in recent years in hospital episode statistics in the UK (25), although there have been no similar recent studies examining the accuracy of death certification. A further weakness is the fact that we restricted our analysis of avoidable deaths to the first 365 days following discharge, whereas an appreciable proportion of avoidable deaths may occur over a longer period, thereby underestimated in our analysis. However, a number of studies have found that this is the period of highest mortality risk in SMI (18) and arguably one where interventions might have particular impact in reducing the mortality gap (3). Third, our study only focused on investigating avoidable mortality risk in people who had been admitted with a diagnosis of schizophrenia or bipolar disorder, and it could be argued that our methods may have over-estimated the risk from these conditions as we could not include people who had not been recently admitted. However, we would argue that in these specific groups, the mortality gap has been shown to be increasing (4–6), and thus, the need for further research and intervention is most pressing (3, 26). Finally, whilst we were able to examine the effect of age and sex differences on avoidable causes of death, we were not able to examine the impact of some other important determinants of mortality in our analysis including ethnicity and duration of mental illness, as information on these variables are not collected within our data set (2). Thus, we recommend that any further research on avoidable causes of death in these populations should also collect information on these determinants and quantify their effects on avoidable mortality.

Meaning of the study

Our study indicates that avoidable mortality is an important component of death in people with schizophrenia and bipolar disorder who have recently been discharged from inpatient care, especially deaths potentially amenable to high-quality medical care. There are a number of possible explanations for our findings including higher risks of physical illness associated with SMI, reduced access to care and/or worse care provision (27). Further explanations include the possibility of premature discharge from inpatient care with untreated or partially treated physical illness and/or challenges with adherence to or less adequate provision of medical or surgical follow-up resulting in greater risk of death from avoidable diseases. Higher risks of incident physical illness following discharge may be directly related to underlying mental disorders, may be compounded by co-existing alcohol or substance abuse or may be an adverse effect of treatments given. Finally, higher mortality may be a result of poorer care when admitted with physical illness (27).

Our hypothetical SMRs show that even with reductions in all avoidable causes of death (including suicide) down to expected levels the mortality gap was not reduced completely. This may reflect a wider increase in risk of disease associated with SMI, not just for those diseases for which death is deemed avoidable. It is also possible that current definitions of avoidable causes of death have lower specificity in these populations at high risk of mortality. We suggest that further research is needed

to quantify the sensitivity and specificity of these definitions of avoidable causes of mortality in these populations by comparing population-based estimates with estimates from studies utilising information from clinical case reviews or confidential inquiries.

Our study indicates that investment to tackle avoidable causes of mortality, especially those potentially amenable to medical care and underlying socio-economic inequalities could have a large effect in reducing the mortality gap, at least in the first year after discharge. We welcome the current government's focus on reducing premature mortality in the UK (28), and our findings suggest that their focus on reducing physical illness in those with mental illness is an appropriate approach to narrow the recognised mortality gap.

Declaration of interest

None.

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Appendix 2 - Literature review of mortality studies in those with schizophrenia and bipolar disorder over the past decade

Reference	Type of study	Countries reported	Study period*	Conditions studied, and numbers included	Age groups included	Mortality risk estimate	Summary
(Lawrence, Kisely et al. 2010)	Systematic review						Systematic review of mortality studies in mental illness over the last 30 years, intended to update Harris and Barraclough's original systematic review in 1997(Harris and Barraclough 1997; Harris and Barraclough 1998). They suggest from their review of the existing evidence that the mortality gap is increasing as a result of people with mental illness not benefitting from advances in healthcare seen in the general population.
(Ilgen, Bohnert et al. 2010)	Cohort study VA hospital admissions data	US	1999-2006	3 million people who used VA services	>18 years	See summary	Found that men with bipolar disorder (HR=2.98) and women with substance abuse (HR=6.62) were particularly at risk of suicide.
(Dutta, Murray et al. 2010)	Retrospective cohort Hospital admissions data	UK	1965-2004	2723 people with first episode of psychosis	16-86 years	All-cause SMR for 1st episode psychosis = 1.84	Found that the case fatality from suicide was considerably lower than in previous published research, but the risk of suicide persisted even a decade after 1st presentation, with mean time to suicide of 5.6 years.
(Wildgust and Beary 2010)	Literature review	974 references included	1987-2010	-	-	-	Literature review that found an increasing number of recent studies suggesting people with schizophrenia are dying from modifiable causes, however they found few prospective studies that looked at interventions to lower modifiable risks.
(Bushe, Taylor et al. 2010)	Literature review	101 references included	2006-10	-	-	-	Review of research from 2006 on mortality in people with schizophrenia, especially examining four specific questions; whether mortality rates are declining, what the causes of death are, the effects of antipsychotic treatments on mortality and whether these data inform as to how mortality may be reduced in the future. They found that the mortality gap with the general population increased from the 1970s but may have peaked in the mid-1990s. Mortality was dependent upon the age of the cohort, length of follow up and type of study. Antipsychotic treatments reduced mortality when

							compared with no treatment and atypical antipsychotics did not appear to increase cardiovascular mortality and morbidity compared with conventional anti-psychotics.
(Mitchell and Lord 2010)	Systematic review	17 references included	1965-2010	-	-	-	Systematic review of studies that examined medical procedures in people with schizophrenia, and a pooled analysis of prescribed medication in those with and without comorbid mental illness, focusing on those which recruited individuals with schizophrenia and measured mortality. Six of eight studies examining the adequacy of cardiac procedures found lower than average provision of medical care and two studies found no difference. Meta-analytic pooling of nine medication studies showed lower than average rates of prescribing for cardiovascular drugs. There were ten studies linking poor quality of care and possible effects on mortality in specialist settings. In half of the studies there was significantly higher mortality in those with mental ill health compared with controls, although there was inadequate data to confirm a causative link. They concluded that the quality of medical treatment provided to those with cardiac conditions and comorbid schizophrenia is often suboptimal and may be linked with avoidable mortality.
(Chang, Hayes et al. 2010)	Prospective case register study	SE London, England	2007-09	31,719 people with SMI	>15 years	All cause SMR for SMI = 2.15	Found high SMRs for those who accessed services between 2007 to 2009, and also suggested that mortality differs substantially with age, diagnosis, gender and ethnicity.
(Bowers, Banda et al. 2010)	Systematic review	98 references included	1960-2008			No relative risks or SMRs reported	Systematic review of suicides in psychiatric inpatients. Found that suicide rates and demographic features connected to suicides varied substantially between articles, suggesting that there are distinct subgroups of people committing suicide (e.g., people with depression vs. schizophrenia) with differing epidemiological characteristics and contributing determinants. They also confirmed that early in the admission is a high-risk period for suicide, but that the risk of suicide declines most slowly for people with schizophrenia. They also found that the timing and location of suicides seem to be associated with absence of support, supervision, and the presence of family conflict

(Hunt, Windfuhr et al. 2010)	Prospective case register study National suicide register	England & Wales	1997-2006	1,851 absconded from an in-patient psychiatric ward	All ages	No relative risks or SMRs reported	Found that 469 people died after absconding from the ward. Schizophrenia was the most common diagnosis. Absconders were proportionally more likely than current in-patients on agreed leave to have been legally detained for treatment, non-compliant with medication, and to have died in the first week of admission
(Brown, Kim et al. 2010)	Cohort study Hospital admissions list	Southampton, England	1981 – present	370 people with schizophrenia living in the community	16-65 years	All cause SMR for schizophrenia = 2.89	Found a higher rate of all-cause mortality, with unnatural deaths concentrated in the first five years of follow-up. They also suggested that there was an indication that cardiovascular mortality may have increased relative to the general population over the course of the study
(Baandrup, Gasse et al. 2010)	Case control study Hospital admissions list	Denmark	1996-2006	193 people with schizophrenia who died of natural causes and 1937 matched controls who did not die	18-53 years	See summary	Found that the use of anti-psychotics with long half-lives was associated with increased mortality (OR=1.78), but concurrent use of a number of anti-psychotics did not increase mortality above monotherapy (OR=1.48)
(Lu and Lin 2010)	Routine data analysis Death certificate data	Taiwan and US	2003-2005	No absolute numbers quoted	All ages	No relative risks or SMRs reported	Found six-fold difference in mortality rates depending on how psychiatric conditions were selected from death certificates and the mortality differences between the countries increased over the period of the study, except for dementia.
(Nielssen, Glozier et al. 2010)	Retrospective cohort study Hospital admissions list	Australia	1992-2007	160 people who attempted suicide by jumping.	All ages	No relative risks or SMRs reported	Found a large proportion diagnosed with a psychotic illness
(Kiviniemi, Suvisaari et al. 2010)	Cohort study Hospital admissions list	Finland	1995-2000	7591 people with schizophrenia	All ages	All-cause SMR for schizophrenia = 4.45	Found regional differences in mortality, unrelated to population characteristics or psychiatric health service resources
(Isaac and Koch 2010)	Meta-analysis	23 trials	-			See summary	Meta-analysis of 23 phase 2/3 RCTs looking at mortality in people with schizophrenia within 30 days after starting anti-psychotic treatment. Found no significant difference in all-cause mortality between treatment group and controls (OR=1.58)

(Kelly, McMahon et al. 2010)	Cohort study Hospital admissions list	US	1994-2004	1686 people with schizophrenia +/- treated with clozapine.	20-69 years	All-cause SMR for people with schizophrenia on clozapine = 4.7	Found no evidence to suggest that clozapine increased the risk of mortality compared with standard treatment.
(Roshanaei-Moghaddam and Katon 2009)	Systematic review	17 references included	1959-2007			-	Systematic review of studies on bipolar disorder and medical mortality. Included studies with people who require inpatient psychiatric care, or treatment with lithium, or schizoaffective disorder. Found bipolar spectrum disorders are associated with increased premature mortality secondary to general medical illnesses.
(Tiihonen, Lonnqvist et al. 2009)	Cohort study Community sample	Finland	1996-2006	66,881 people with schizophrenia taking anti-psychotics	All ages	See summary	Found that longer cumulative exposure to anti-psychotics (HR=0.81), especially with clozapine (HR=0.74) and second generation anti-psychotics was associated with higher survival rates
(Alaraisanen, Miettunen et al. 2009)	Cohort study 1966 Finnish birth cohort	Finland	1966-97	10934 people from a birth cohort, 100 with schizophrenia	>16 years	OR for suicide in people with schizophrenia = 2	Found that suicide accounts for half of all deaths in people with schizophrenia, more so in the first 3-years.
(Reutfors, Brandt et al. 2009)	Case cohort study Hospital admissions list	Sweden	1984-2000	84 people with schizophrenia who died from suicide and 84 matched controls who did not die	<65 years	See summary	Found that higher educational attainment (OR=3), older age at onset of symptoms (OR=4.8) and history of deliberate self harm (OR=5) were significantly associated with subsequent suicide
(Weinmann, Read et al. 2009)	Systematic review	12 references included	1966-2008				Review of mortality in people with schizophrenia on anti-psychotic medications
(Copeland, Zeber et al. 2009)	Cohort study Primary care clinics list	US	2002-05	241,466 people with schizophrenia, DM, or schizophrenia + DM	>50 years	See summary	Found that those who attended primary care less often had worse mortality outcomes regardless of comorbidity (OR=3.8)
(Rantanen, Koivisto et al. 2009)	Cohort study Hospital admissions list	Finland	1980-1998	23,959 first admissions for schizophrenia	15-65 years	See summary	Found a reduction in overall 5-year mortality among people hospitalized in 1995-1998 (OR=1) compared to people hospitalized in 1980-1984 (OR=0.9).

(Hawken, Crookall et al. 2009)	Cohort study Hospital admissions list	Canada	1985-2005	50 people with schizophrenia and polydipsia, and 40 comparators.	All ages	See summary	Found that polydipsia predicted mortality in people with schizophrenia (HR=2.84).
(Laursen, Munk-Olsen et al. 2009)	Cohort study National psychiatric register	Denmark	1994-2007	4.6 million people with SMI.	All ages	HR for CVD mortality in people with SMI = 2.9	Found a negligible excess rates of healthcare contacts for heart disease in people with SMI, compared with a large increase in risk of mortality from heart disease
(Kilbourne, Morden et al. 2009)	Cohort study VA hospital admission list	US	1999-2006	147,193 people with SMI	All ages	See summary	Found that people with schizophrenia (HR=1.17) or other psychotic disorders (HR=1.3) were more likely to die from IHD than those without mental illness.
(Tran, Rouillon et al. 2009)	Cohort study Hospital admissions list	France	1993-2004	3470 people with schizophrenia	18-64 years	All-cause SMR for schizophrenia = 3.6	Found that cancer was the second most frequent cause of mortality, especially lung cancer in men and breast cancer in women
(Chong, Tay et al. 2009)	Cohort study Hospital admissions list	Singapore	1999-2006	608 people with schizophrenia	>29 years	See summary	Found increased risk of mortality in people with tardive dyskinesia (HR=1.9)
(Abrams, Vaughan-Sarrazin et al. 2008)	Cohort study VA hospital admission list	US	2004	31,218 people with principal diagnosis of CCF or pneumonia with/ without psychiatric comorbidity.	All ages	See summary	Found that the method used to identify psychiatric comorbidities in acute medical populations has a strong influence on the rates of identification and the associations between psychiatric illnesses with hospital mortality (OR of death from CVD with psychiatric comorbidities between 0.59 – 1.04,OR of death from pneumonia with psychiatric comorbidities between 0.81-1.17)
(Koponen, Alaraisanen et al. 2008)	Literature review	64 references included	1966-2007	-	-	-	Literature review of sudden CVD mortality in people with schizophrenia
(McGrath, Saha et al. 2008)	Systematic review	38 references with SMR data	1965-2006	-	-	All-cause SMR for schizophrenia for the duration of the study = 2.6	Systematic review of incidence, prevalence and mortality in people with schizophrenia. Concluded that people with schizophrenia have a 2-3 fold risk of dying, and this differential mortality gap has increased over

							recent decades, SMR 1970s = 1.8, 1980s = 3.0, 1990s = 3.2
(Ran, Chan et al. 2008)	Cohort study Community survey	Chengdu province, China	1994-2004	510 people with schizophrenia	>15 years	All-cause SMR for schizophrenia = 4	Found that people with schizophrenia of all age groups had a marked increase in mortality and suicide.
(Tokuda, Obara et al. 2008)	Cohort study Hospital discharge list	Japan	1987-2004	1108 people with schizophrenia	All ages	All-cause SMR for schizophrenia = 1,29	Found that the leading causes of death were suicide, malignant lymphoma or leukemia, stroke, and sepsis
(Honkonen, Mattila et al. 2008)	Cohort study Hospital discharge list	Finland	1999-2005	3835 former psychiatric inpatients.	18-64 years	All-cause SMR for schizophrenia = 3.93	The SMRs for unnatural causes were higher than those for natural causes. The highest SMRs for unnatural causes of death were found in patients with mood disorders and the highest SMRs for natural causes of death in people with schizophrenia spectrum disorders
(Hiroeh, Kapur et al. 2008)	Cohort study National psychiatric register	Denmark	1973-93	4.1 million people with SMI	>15 years	All-cause SMR for schizophrenia = 2.1 (men), 1.9 (women)	Found the highest cause-specific SMRs for people with SMI were for nervous system diseases, gastrointestinal diseases, lung diseases, and "all other natural causes"; the lowest were for neoplasm
(McGirr and Turecki 2008)	Case control study Post-mortem lists	Canada	-	527 consecutive suicides in people with/ without schizophrenia	All ages	See summary	Found people with schizophrenia who had committed suicide were likely to be younger (mean = 32 years) more likely to have attended university (OR=2.12), less likely to be married (OR=0.09) and have increased levels of impulsive aggressive behaviours, compared to people without schizophrenia.
(Tidemalm, Waern et al. 2008)	Cohort study Hospital admission list	Sweden	1997-2000	12,103 people with SMI.	All ages	All-cause SMR for SMI in 1998-2000 = 3.3 (men), 2.3 (women)	Before-after study of the effects of a community mental healthcare reform program. Nil effect found on mortality
(Haukka, Tiihonen et al. 2008)	Cohort study Hospital admission list	Finland	1997-2003	1611 people with schizophrenia	>16 years	See summary	Found anti-psychotic use was associated with significant reduced mortality from suicide (HR=0.52), either alone or in combination with anti-depressants
(Capasso,	Cohort study	Minnesota	1950-	319 people with	All ages	No relative risks or	Found that there was no narrowing of mortality gap

Lineberry et al. 2008)	Outpatient list	US	2005	schizophrenia		SMRs reported	over the course of the study
(Hamer, Stamatakis et al. 2008)	Cohort study Hospital admission list & community survey	Scotland	1995-2006	597 people admitted with SMI	>16 years	All-cause HR for SMI = 3.25	Found that mortality was mediated by behavioural risk factors such as socioeconomic status (OR=2.17), history of smoking (OR=4.69) and poor level of physical activity (OR=2.24).
(Kisely, Sadek et al. 2008)	Cohort study Hospital admission list	Canada	1995-2001	247,344 people with SMI	All ages	RR for cancer mortality in SMI = 1.59	Found an increased cancer mortality, but no evidence of increased incidence
(Saha, Chant et al. 2007)	Systematic review	25 countries	1980-2006	-	-	Median all-cause SMR for schizophrenia = 2.58	37 articles from 25 countries over 25 years reviewed to identify trends in all-cause mortality for people with schizophrenia. They found a consistent increased risk of mortality in people with schizophrenia compared with the national populations, and also mortality rates have increased in recent decades
(Pirkola, Sohlman et al. 2007)	Cohort study Mental health service mapping data	Finland	1985-2001	428 mental health service providers mapped against national suicide mortality rates	-	See summary	Found that suicide risk had decreased during the study (RR between 1985-91 & 1995-2001=1.25-1.5), and that well-developed community mental-health services are associated with lower suicide rates
(Hunt, Kapur et al. 2007)	Case control study National suicide dataset	England & Wales	1999-2000	222 people who died of suicide while in psychiatric in-patient care and matched living controls.	16-65 years	See summary	Previous deliberate self-harm (OR=4.3), recent adverse life events (OR=2), and symptoms of depressive illness at last contact (OR=2) were associated with increased risk of suicide.
(Dutta, Boydell et al. 2007)	Cohort study Outpatient & admission list	SE London, England	1965-99	235 people with first diagnosis of bipolar disorder.	All ages	SMR from suicide for bipolar disorder = 9.77	Found that suicide is significantly increased, but actual case fatality was not as high as previously seen in the literature. Alcohol abuse (HR=6.7) and deterioration in premorbid functioning (HR=5.2) were associated with increased risk of suicide
(Laursen, Munk-Olsen et al. 2007)	Cohort study National	Denmark	1973-2001	5.5 million with SMI	All ages	All-cause RR for schizophrenia = 1.7-13.4 (men),	Found the rate of natural deaths is higher in people with schizophrenia than other psychiatric conditions, and family history of psychiatric admission was associated

	psychiatric register					1.5-29.7 (women), All cause RR bipolar disorder = 1.5-10 (men), 1.4-25 (women)	with excess mortality
(Amaddeo, Barbui et al. 2007)	Cohort study Outpatient & admission list	Italy	1982-2001	6,956 people with SMI	>14 years	SMR avoidable mortality in SMI = 4.31	Found high rates of preventable mortality in people with SMI compared with general population.
(Limosin, Loze et al. 2007)	Cohort study Hospital admission list	France	1993-2003	3470 people with schizophrenia	All ages	All-cause SMR for schizophrenia = 3.7 (men), 4.5 (women)	Found that male gender, (HR=2.03), previous suicide attempts, history of drug abuse and short duration of illness all predicted suicide attempts.
(Pompili, Amador et al. 2007)	Literature review						Literature review of suicide in people with schizophrenia
(Fors, Isacson et al. 2007)	Cohort study Community survey	Sweden	1991-2001	255 people with schizophrenia and 1275 matched comparators	>18 years	All-cause HR in people with schizophrenia = 1.81	Found high rates of mortality for unnatural causes and CVD, especially for those living in urban areas
(Auquier, Lancon et al. 2007)	Literature review						
(Simon, Hunkeler et al. 2007)	Cohort study Health insurance records	US	1994-2001	32,360 people with bipolar disorder	All ages	See summary	Found that the risk of suicide death is significantly related to female sex (HR of suicide for men=0.68) and comorbid anxiety disorder (HR=1.81).
(Khan, Schwartz et al. 2007)	Cohort study Data from trials of atypical anti-psychotics	-	1982-2002	16,791 people with schizophrenia	>18 years	OR of death in people with schizophrenia on anti-psychotics versus not = 0.23	Found no evidence of increased risk of death in those with schizophrenia taking antipsychotics, compared with placebo group
(Barak, Baruch et al. 2007)	Cohort study Hospital	Israel	1990-2005	3111 elderly people with SMI	>65 years	No relative risks or SMRs reported	Found no evidence of increased adverse medical outcomes including incidence of stroke, CVD and mortality in those with SMI on anti-psychotics

	admission list						
(Plomondon, Ho et al. 2007)	Cohort study VA hospital admission list	US	2003-05	14,194 with admission for acute coronary syndrome (ACS)	All ages	HR for all-cause mortality in people with SMI and ACS, versus no SMI = 0.91 (not significant)	Found increased level of SMI in those with ACS, but no association between SMI and ACS mortality
(Osborn, Levy et al. 2007)	Cohort study General practice research database	UK	1987-2002	46,136 people with SMI and 300,426 matched comparators	All ages	HR for CVD in those with SMI = 1.1 - 3.2, HR for stroke in those with SMI = 1.3 – 2.5	Found high risk of CVD, and stroke deaths in those with SMI not explained by the presence of common risk factors including anti-psychotic drug use, smoking or social deprivation
(Kapur, Hunt et al. 2006)	Prospective case register study National hospital discharge records	England & Wales	1997-2003	No absolute numbers given	>15 years	Likelihood ratio for suicide rates in people with schizophrenia between 1997-03 = 19.54 ($p<0.001$)	Study tracking trends in in-patient and post-discharge suicide. Found a fall in rate of inpatient and post-discharge suicide
(Hunt, Kapur et al. 2006)	Retrospective cohort study National suicide dataset	England & Wales	1996-2000	20,927 people who committed suicide who had been in contact with mental health services in last year	All ages	No relative risks or SMRs reported	Found that people with schizophrenia who committed suicide were more likely to be young, male, unemployed and from ethnic minority. There was a high likelihood of violent method of suicide in people with schizophrenia.
(Goldacre, Duncan et al. 2006)	Cross-sectional, routine record study Death certificates	England	1979-99	No absolute numbers given	All ages	No relative risks or SMRs reported	Study reporting trends in the recording of psychiatric diagnosis on the death certificates. Found that mortality associated with psychiatric illness is greatly under-estimated if only the underlying cause is taken into account. Also found that the trend in psychiatric diseases on the death certificates varies between disease over time, with a decline in mortality rates for schizophrenia, and an increase for depression and dementia on death certificates between 1979 to 1999.
(Healy, Harris et al. 2006)	Cohort study Hospital admission list	Wales	1875-1998	1279 people admitted with psychosis	All ages	No relative risks or SMRs reported	Comparison of suicide rates before and after introduction of chlorpromazine in north-west Wales. Found that suicide rates per hospital admission were twenty times higher between the first and last surveys

(Colton and Manderscheid 2006)	Cohort study Hospital admission list	8 states, US	1997-2000	No absolute numbers given for people with SMI included	All ages	All cause SMR for SMI between 1.8-4.9, YPLL between 13.5-32.2	Found increase mortality especially from natural causes in all states, and widespread variation between states
(Kurihara, Kato et al. 2006)	Cohort study Hospital admission list	Bali	1990-2001	59 consecutive admissions for schizophrenia	All ages	All-cause SMR for schizophrenia = 5.98	Letter giving data on death rates for people with schizophrenia
(McGirr, Tousignant et al. 2006)	Case control study Post-mortem list	Canada	-	85 people who died of suicide with schizophrenia and matched controls who did not commit suicide	All ages	See summary	Found that the presence of depressive illness (OR=395), moderate to severe psychotic symptoms (OR=87) and a family history of suicidal behaviour (OR=16) most readily predicted risk of suicide
(Joukamaa, Heliovaara et al. 2006)	Cohort study Community survey	Finland	1978-97	7,217 people with mental illness	>30 years	RR of mortality in schizophrenia = 2.84	Follow-up to study published in 2001. Found that mortality in people with schizophrenia was increased compared with others in the cohort, and taking into account a number of confounding variables. Antipsychotics had a graded effect on mortality depending on dose
(Copeland, Zeber et al. 2006)	Retrospective cohort study Post-mortem list	US	2001-02	27,798 deaths in former attended at VA hospital.	All ages	OR for unforeseen deaths = 2.4	Found that death from unforeseen causes was more common in people with schizophrenia
(Miller, Paschall et al. 2006)	Cohort study Hospital admission list	Ohio, US	1998-2002	20,018 people with SMI	>18 years	All-cause SMR for SMI = 3.2, YPLL = 32 +/- 12.6	Found high SMR and YPLL, especially for heart disease and suicides
(Craig, Ye et al. 2006)	Cohort study Hospital admission list	US	1989-95	567 people with first onset psychosis	15-60 years	No relative risks or SMRs reported	Found these people experience similar patterns of mortality over the first 10 years after the index admission regardless of the underlying diagnosis
(Ward, Ishak et al. 2006)	Cohort study Data from prescribing	Canada	1999-2004	45,045 people with schizophrenia who were prescribed anti-psychotic medications	>15 years	HR for all-cause mortality in those with good versus poor compliance =	Found that good compliance with atypical antipsychotic medications was associated with substantial reductions in the risk for all-cause and psychosis-related hospitalizations

	database					0.58	
(Tsai, Lee et al. 2005)	Case control study Hospital admission list	Taiwan	1987-2002	60 deceased people with bipolar disorder and matched living controls	24-83 years	See summary	Found that antipsychotic treatment prior to the last visit (OR=0.87), serum alanine aminotransferase levels (OR=1.13), and leukocyte counts (OR=1.58) were all associated with the risk of death from natural causes
(Goff, Cather et al. 2005)	Literature review						Literature review of physical illness in those with SMI and clinical guidelines for management of modifiable risk factors for mortality
(Rasanen, Hakko et al. 2005)	Cohort study Hospital admission list	Finland	1992-2001	253 long-stay psychiatric patients	25-88 years	See summary	Found that deaths due to avoidable conditions caused about 30% of all deaths, SMRs from avoidable deaths being 1.9 (males) and 3.2 (females).
(Kuo, Tsai et al. 2005)	Case control study Hospital admission list	Taiwan	1985-2001	78 case-comparator pairs of people with schizophrenia who did/ did not commit suicide	All ages	See summary	Found depressive symptoms (OR=23), and higher suicide intensity (OR=2.8) were significant predictors of suicide
(Drew 2005)	Cohort study Hospital admission list	Central Australia	1985-2000	19059 people with SMI	All ages	All-cause SMR for SMI = 1.08	Found increased rate of suicide, but overall mortality not obviously increased
(Desai, Dausey et al. 2005)	Cohort study VA hospital admission list	US	1994-98	121,933 people with SMI	All ages	No relative risks or SMRs reported	Found that suicide was associated with short length of inpatient stay, poor continuity of care and lack of readmission in 6 months
(Kisely, Smith et al. 2005)	Cohort study Community and primary care lists	Canada	1995-2000	221,048 people with SMI	All ages	All cause SMR for schizophrenia = 2.2, for SMI = 1.7	Found that mortality rate is increased in all people with SMI, not just in-patients
(Heila, Haukka et al. 2005)	Cohort study National hospital discharge list	Finland	1980-96	58,761 people discharged with schizophrenia	All ages	All cause SMR for schizophrenia = 2.9	Found no noticeable increase in mortality between 1980-96, despite rapid decrease in the number of hospital beds

(Muller, Barkow et al. 2005)	Cohort study	Germany	-	500 people with SMI	All ages	See summary	Found that suicide attempts were associated with poor premorbid adjustment (OR=2.1), low age of onset (OR=0.95), low Goal Attainment Scaling (GAS) scores (OR=0.95) and childlessness in females (OR=2.5)
(Hawton, Sutton et al. 2005)	Systematic review					See summary	Review of the risk factors for suicide in schizophrenia. 29 case-control/ cohort studies included. Found evidence that previous depressive illness (OR=3), previous suicide attempts (OR=4), drug misuse (OR=3.2), agitation (OR=2.6), fear of mental disintegration (OR=12.1) and recent loss (OR=4) were all associated with increased risk of suicide
(Pompili, Mancinelli et al. 2005)	Literature review						Literature review focused on where people with schizophrenia commit suicide. Found that 50% of suicides occurred during inpatient care, especially amongst the young, childless, and those with a history of multiple admissions, and paranoid subtype
(Sinclair, Mullee et al. 2004)	Case control study Post mortem records	Wessex, England	1988-97	51 people with schizophrenia who committed suicide and 82 controls who did not	All ages	See summary	Found that depressive symptoms (OR = 2.6) and previous suicide attempts (OR= 2.7) are significant predictive factors
(Kelly, Shim et al. 2004)	Retrospective cohort study Post mortem records	US	1989-98	97 people with schizophrenia who died between 1989-98	All ages	No relative risks or SMRs reported	Found that those who died of suicide experienced both higher positive and negative psychological symptoms
(Bourgeois, Swendsen et al. 2004)	Randomised controlled trial	11 countries	-	980 patients with schizophrenia or schizoaffective disorder	>33 years	HR for suicide in people with awareness of symptoms = 1.17 (non-significant)	Trial to find out what the effect of increasing awareness has on the suicide rates. Found a positive but complex relationship between awareness and suicide risk
(Barak, Mirecki et al. 2004)	Cohort study Hospital admission list	Israel	1998-2002	756 people with schizophrenia.	All ages	OR of suicide in people with schizophrenia not taking a SGA = 3.5	Study of the effect of second generation anti-psychotics on 5 year suicide rates. Found that risperidone and olanzapine may have some protective effects over 5 years. Effects differ between different second generation anti-psychotics
(Casey, Haupt	Literature review						

et al. 2004)							
(Yim, Yip et al. 2004)	Case control study Hospital admission list	Hong Kong	1996-99	73 people with SMI who committed suicide and 73 matched controls from the same ward who did not commit suicide	All ages	See summary	Found increased risk of death from suicide post psychiatric hospital discharge, clustering in the first 30 days, associations with unemployment (OR=12), past suicide attempts (OR=3.4), maternal mental illness (OR=13.4) and suicide ideation (OR=5)
(Pompili, Girardi et al. 2004)	Literature review						Literature review on the subject of suicide in people with schizophrenia
(Enger, Weatherby et al. 2004)	Cohort study Research database	US	1995-99	1920 people with schizophrenia and 9600 matched comparators	All ages	HR = 4.4 for mortality in people with schizophrenia compared with controls	Found that users of typical antipsychotics had a five-fold increased risk of myocardial infarction than controls
(Vythilingam, Chen et al. 2003)	Cohort study Hospital admission list	US	1977-90	110 depressed clients +/- psychotic symptoms	All ages	HR = 2.3 for people with psychotic symptoms compared to non-psychotic	Found that people with psychotic depression have a two-fold greater risk of mortality than do patients with severe, non-psychotic depression
(Desai and Rosenheck 2003)	Cohort study VA hospital admission list	US	1991-99	5352 long stay psychiatric patients	All ages	No relative risks or SMRs reported	Found that the delivery of inpatient mental health services by the VA had changed dramatically during the 1990s. They also found no substantially adverse changes in mortality rates or in the extent to which long-term inpatients remain connected with the VA system after discharge.
(Harkavy-Friedman, Kimhy et al. 2003)	Cohort study Hospital admission list	US	1995-2001	100 people with schizophrenia	All ages	No relative risks or SMRs reported	Study investigating the role of command hallucinations on suicide. Found that command hallucinations did not predict subsequent suicide
(Herings and Erkens 2003)	Cohort study Pharmacy & hospital records	Holland	1996-2000	604 people with psychosis.	15-45 years	RR of suicide in people that have drug holidays compared to no drug holidays= 4.2	Found that people who do not refill atypical antipsychotics in time can be identified from pharmacy records and are likely to be at increased risk of death from suicide

(Stark, MacLeod et al. 2003)	Cohort study Hospital discharge list	Scotland	1977-94	6776 people discharged from long stay psychiatric in-patient care with SMI	>15 years	All-cause SMR for SMI = 1.6	Found that death rates from both natural and unnatural causes of death were increased
(Duggan, Warner et al. 2003)	-	UK	-	-	-	No relative risks or SMRs reported	Methods paper offering a model to compare current levels of clozapine prescribing with a scenario in which all suitable clients with treatment-resistant schizophrenia received clozapine. Suggest that 53 lives could be saved in the UK each year. Concluded that the use of clozapine in treatment-resistant schizophrenia saves lives, frees resources and is cost-effective.
(Hawton, Zahl et al. 2003)	Prospective case register study	Oxford, England	1978-97	11583 people who had undertaken deliberate self-harm	All ages	RR of suicide in 1st year after episode of DSH = 66	Found that there was a significant and persistent risk of subsequent suicide, which varies by age and sex. However mortality had not changed for this group over the period of the study
(Morgan, Scully et al. 2003)	Cohort study Outpatient & admission list	Ireland	1992-99	72 people with schizophrenia followed-up for 7 years	20-83 years	All-cause SMR for schizophrenia = 2.1	Found a higher all-cause mortality rate in those with schizophrenia
(Rasanen, Hakko et al. 2003)	Cohort study Hospital admission list	Finland	1992-2000	253 consecutive long-stay psychiatric patients	30-90 years	All-cause SMR for SMI = 4.3	Found that SMR was highest for young age groups. SMR decreases in older age groups
(Pinikahana, Happell et al. 2003)	Literature review		1990-99				Literature review of suicide in people with schizophrenia
(D'Avanzo, La Vecchia et al. 2003)	Cohort study Hospital admission list	Northern Italy	1994-2000	2915 people admitted with SMI	20-94 years	All-cause SMR for SMI = 2.5 (males), 2.4 (females)	Found high all-cause mortality, but no excess deaths for cancer
(Lawrence, Holman et al. 2003)	Cohort study Outpatient & admission list	Western Australia	1980-1998	210,129 mental health service users	All ages	SMR for IHD in people with SMI over the period of the study = 1.9 (men), 1.9 (women)	Found little difference in hospital admission rates for IHD between psychiatric patients and the general community, but much lower rates of revascularisation procedures, particularly for people with psychoses. Also found mortality rate from IHD in psychiatric patients did not diminish over time compared to the general population

(Montout, Casadebaig et al. 2002)	Cohort study Outpatient & admission list	France	1993-97	3474 people with schizophrenia	All ages	OR for all deaths = 1.6 in those taking thioxanthine versus those taking phenothiazine	Found increased risk of death in those taking thioxanthine
(Salokangas, Honkonen et al. 2002)	Cohort study Hospital admission list	Finland	1982-94	4338 people with schizophrenia	All ages	Proportions of deaths in people discharged with SMI = 5% (1980), 4.5% (1986), 6.4% (1990), 4.9% (1994), p value for trend = 0.38	Study of four cohorts of people with schizophrenia admitted between 1982 to 1994. Found that despite decreasing bed numbers, mortality had remained the same for this population over the period of the study
(Nordentoft, Jeppesen et al. 2002)	RCT	Denmark	1998-2000	341 people with a first-episode schizophrenia randomised	18-45 years	Chi-sq for difference in suicidal thoughts after one year in treatment and control groups = 0.003, p= 0.96	Study of integrated treatment versus treatment as usual to decrease 1 year post discharge suicide. Found no reduction in suicide attempts at 1-year in treatment group compared with controls
(Kreyenbuhl, Kelly et al. 2002)	Case control study Post-mortem records	US	1989-98	15 people who committed suicide with schizophrenia and 100 matched controls without schizophrenia	All ages	No relative risks or SMRs reported	Utilised informant interviews to compare circumstances around the suicides. Found higher rates of depressive symptoms and more violent suicidal acts in those with schizophrenia
(Angst, Stassen et al. 2002)	Cohort study Hospital admission list	Switzerland	1959-97	406 consecutive admissions with depressive disorder	All ages	All-cause SMR for bipolar disorder = 1.58	Found increased SMR for suicide and CVD
(Politi, Piccinelli et al. 2002)	Cohort study	Pavia, Italy	1978-94	2148 consecutive admissions for SMI	All ages	SMR all-causes for SMI = 4.6 (men), 3.4 (women)	Found high all-cause mortality. Trend towards decreasing mortality over time, falling by 29% over the period of the study
(Harrison, Hopper et al. 2001)	Cohort study	18 countries	-	15 and 25 yr outcomes in people with schizophrenia.	All ages	All-cause SMR for schizophrenia varied from 0 to 8.8	Found that about 50% of surviving cases had favourable outcomes, but there was marked heterogeneity across geographic centres. Concluded that a significant proportion of treated incident cases of

							schizophrenia achieve favourable long-term outcome. Sociocultural conditions appear to modify long-term course.
(Pérez-Cárceles, Inigo et al. 2001)	Retrospective cohort study Prison psychiatry list	Alicante, Spain	1984-97	64 deaths in people with SMI in psychiatric prison	18-74 years	No relative risks or SMRs reported	Study of mortality in people maximum security prison with SMI in Spain. Found an association between cause of death and age
(Druss, Bradford et al. 2001)	Cohort study Medicare enrolees	US	1994-95	88241 medicare patients who were hospitalized for clinically confirmed acute myocardial infarction	65+ years	HR for 1 year mortality = 1.10 (95% CI 0.96-1.26) after controlling for quality indicators	Study looking at the mortality one year after myocardial infarction in people with/ without SMI. Hazards rates calculated for differing levels of 5 established quality indicators. Found that deficit in quality care explained a substantial proportion of the mortality seen
(Hansen, Jacobsen et al. 2001)	Cohort study Psychiatric hospital register	Norway	1980-92	1998 people admitted with SMI	All ages	All-cause SMR for schizophrenia in 1963-74 = 1.7 (men), 2.3 (women), 1980-92 = 3.0 (men), 2.5 (women)	Found high SMR for all causes in people with SMI, especially cardiovascular disease and suicide compared with rates calculated from a similar sample in earlier periods
(Hiroeh, Appleby et al. 2001)	Cohort study National psychiatric registry	Denmark	1973-93	72,208 people with SMI	>15 years	All-cause SMR for SMI = 6.1 (men), 6.3 (women)	Found increased risk of dying by homicide in men with schizophrenia and those with affective psychosis
(Osby, Brandt et al. 2001)	Cohort study Hospital admission list	Sweden	1973-95	15,386 people with first admission for bipolar disorder	All ages	All-cause SMR bipolar disorder = 2.5 (men), 2.7 (women)	Found increased mortality, especially in the first year after diagnosis
(Joukamaa, Heliovaara et al. 2001)	Cohort study Community survey	Finland	1977-97	7,217 people with mental illness	>30 years	All-cause RR of death for schizophrenia = 3.3 (men), 2.3 (women)	For people with schizophrenia only risk of respiratory disease was increased, RR (men) = 9.5, (women) = 8.3
(De Hert, McKenzie et al. 2001)	Case control study	Belgium	1973-94	63 people who committed suicide with schizophrenia and 63	<30 years	See summary	Found that risk of suicide was higher in males, with chronic relapsing disease (OR=6), depressive symptoms (OR= 36) and previous suicide attempts

	Hospital admission list			people who did not commit suicide.			(OR=11)
(Plocka-Lewandowska, Araszkiewicz et al. 2001)	Cohort study Hospital admission list	Poland	1985-97	32 people with schizophrenia who had had dexamethasone suppression tests	All ages	No relative risks or SMRs reported	Found association between suicide attempts and baseline and post-test cortisol levels, suggesting that hyperactivity of HPA axis may be implicated in suicide risk in people with schizophrenia
(Khan, Khan et al. 2001)	Secondary data analysis FDA database	US	-	10,118 people with schizophrenia involved in RCT studies	All ages	Chi-sq for difference in suicide rates between treatment and controls groups = 0.99 (not significant)	Study of suicide risk in participants with schizophrenia receiving placebo in antipsychotic RCTs. Found that risk of suicide did not differ between treated and placebo groups
(Loas, Yon et al. 2001)	Cohort study Hospital admission list	France	1991-99	150 consecutive people with schizophrenia attending in/out-patients	All ages	Relative risk of suicide death in those with anhedonia = 1.7 (non-significant)	Found that anhedonia is not a significant risk factor for suicide
(Mojtabai, Varma et al. 2001)	Cohort study WHO dataset	India	1978-95	171 first contact psychosis in community clinics	15-54 years	Mortality rate ratio of 9.4 for people with poor 2-year outcomes versus others	Found that poor outcomes at 2 years strongly predicted mortality at 15 years follow-up
(Fontaine, Heo et al. 2001)	Theoretical prospective cohort study	US	1999	Used information from 5209 respondents in the Framingham study to estimate the effects of anti-psychotic weight gain	All ages	Theoretical excess deaths calculated	Suggested that 492 suicide deaths per 100,000 people with schizophrenia would be prevented over 10 years with the use of clozapine compared to 416 additional deaths due to antipsychotic induced weight gain.
(Ray, Meredith et al. 2001)	Retrospective cohort study Medicaid enrolees list	Tennessee, US	1988-93	481,744 medicaid enrolees prescribed anti-psychotic meds.	15-84 years	Relative risk of sudden cardiac death = 2.39 (moderate anti-psychotic users)	Found that moderate doses of antipsychotics had large relative and absolute increases in the risk of sudden cardiac death.
(Babidge, Buhrich et al.	Cohort study	Sydney, Australia	1988-91	708 homeless people, of which 506 had	All ages	SMR for homeless = 3.7 (men), 3.1	Found high rates of mortality in the homeless regardless of the diagnosis of schizophrenia

2001)	Psychiatric clinic list			schizophrenia		(women)	
(Sernyak, Desai et al. 2001)	Cohort study VA hospital discharge abstracts	US	1992-95	2830 people with and 1415 people without schizophrenia, all taking clozapine	All ages	Odds of death for people with schizophrenia exposed to long-term clozapine compared with those with schizophrenia was 0.63	Study of clozapine treatment on 4-yr suicide rates. Found reduced all-cause mortality, mostly from reduced respiratory disease, no significant reduction in suicide rates
(Brown, Beck et al. 2000)	Cohort study Hospital admission list	US	1975-95	6891 consecutive psychiatric outpatients who attended the University of Pennsylvania	All ages	See summary	Found that suicidal ideation (HR=3.87), the presence of major depressive disorder (HR=3.19) or bipolar disorder (HR=3.57) and unemployment status (HR=2.56) predicted risk of suicide
(Brown, Inskip et al. 2000)	Cohort study Community register of people with schizophrenia	Southampton, England	1981-95	370 people with schizophrenia who used psychiatric services between 1981-82 followed up until 1995	16-65 years	SMR for schizophrenia = 2.98 (all causes), 2.32 (natural causes), 12.7 (unnatural causes), 4.7 (avoidable causes)	Found high SMRs for both natural/ unnatural causes of death, especially for smoking related diseases
(Keck, Strakowski et al. 2000)	Literature review						Literature review suggesting that atypical antipsychotics may exert therapeutic effects on depression and hostility as well as psychosis and that clozapine and olanzapine may reduce suicidality in people with schizophrenia
(Hannerz and Borga 2000)	Cohort study National hospital discharge registry	Sweden	1978-85	41,134 people with schizophrenia admitted between 1978-82 and followed-up until 1983-85	All ages	Reduced life expectancy = 22-28% (men), 15-22% (women)	Found that life expectancies varied significantly by age. Suggested that reduction in mortality rates requires different strategies in different age groups and should be targeted at specific causes of death
(Meltzer, Anand et al. 2000)	Literature review						Literature review of suicide risk in people with schizophrenia treated with cloazpine, and outline of methodology for the International Suicide Prevention

							Trial (InterSePT)
(Lawrence, Holman et al. 2000; Lawrence, Jablensky et al. 2000)	Cohort study Mental health services contact list	Western Australia	1980-95	131,105 people with SMI whose first contact with mental health services was between 1980-95	All ages	SMR for SMI = 2.6 (males), 2.2 (females)	Found high all-cause mortality, except for those treated in outpatient facilities. However second study using the same cohort showed no association between SMI and cancer mortality
(Hoyer, Mortensen et al. 2000)	Cohort study Hospital admission list	Denmark	1973-93	54,103 people with affective disorder who attended psychiatric hospital for the first time between 1973-93.	15 years+	SMR suicide for bipolar disorder = 18.09, SMR natural causes for bipolar disorder = 1.5-2.4	Found that mortality for all subgroups with affective disorder was raised.
(Funahashi, Ibuki et al. 2000)	Case control study From list of discharged clients who committed suicide	Nagoya, Japan	1967-92	80 people with DSM3 diagnosis of schizophrenia, schizoaffective disorder or schizotypal personality. Matched to group who committed suicide no evidence of schizophrenia	All ages	No relative risks or SMRs reported	Found that risk of suicide increased in those with high levels of suicidal ideation, and anxiety
(Osby, Correia et al. 2000)	Cohort study Hospital admissions list	Stockholm, Sweden	1979-95	5802 people with first admission for schizophrenia between 1979-95	All ages	1991-1995, SMR for schizophrenia = 9.4 (men), 3.6 (women) 1976-1980, SMR for schizophrenia = 2.6 (men), 2.1 (women)	Mortality rate examined for 4 separate periods. Found increasing admissions for schizophrenia and increasing mortality rates compared the national population, especially for cardiovascular disease

* study period includes the period of participant recruitment and follow-up

Appendix 3 – Methods of data linkage and data extraction

Data linkage methods

The information for this section has been drafted from the description of the methodology of building a national file or health and mortality data published by Leicester Gill (Gill 2004). This methodology is largely still used to construct the linked datasets used in this thesis. Permanent links between hospital records and death records have been created in the dataset to facilitate healthcare outcomes research.

There are three primary stages in linking the health records together. The first stage requires the data to be cleaned and formatted, and the potential match-pairs to be brought together for comparison by sorting the file into various orders. The second stage involves comparing the potential match-pairs to decide whether they belong to the same person. This would generally use a deterministic or a probabilistic matching method. The third stage involves the collation of the person linked records into a person-linked file either by sorting or creating an index in a database system.

The process started with two files, namely the HES datasets supplied by the DH and the mortality dataset supplied by the ONS. HES records for individual patients are stored as Finished Consultant Episodes (FCE), i.e. a period of admitted patient care under a consultant or allied healthcare professional within an NHS trust. Death records are stored as separate files. The first step in data linkage involves reformatting the mortality records were so that the corresponding fields on the ONS mortality record and on the HES record are stored in the same character position in the record. Initially each record was given a different person number, and after the matching and linking has been completed, all records that belong to the same person would have the same person number copied across them.

Next the unmatched HES-ONS file was split into two files. The first file, referred to as the master matching file (MMF) contained only those variables that are used for matching, and

did not contain any clinical or other statistical data. This file was encrypted and stored on a different computing system to the statistical file. Some variables, for example, date of birth, sex and postcode which are required for analysis were aggregated up to age or local authority district level to minimise any attempt to identify an individual from the ensuing analyses. The second file, referred to as the statistical analysis file, contained the variables that are not used for matching but are used for statistical analysis. The two files of HES records were linked together using the unique accession number.

Next a series of computer runs were undertaken to check data quality, including checking the frequency of matching variables and identifying erroneous and outlying values. Records containing such errors were tagged to prevent the erroneous variables being used for matching. Further details of the data quality of the unmatched datasets is published by Gill (Gill 2004).

The first series of matching runs involves matching together all record pairs that have the same NHS number. The file was split into two parts, those with valid NHS numbers and those without. All records having the same NHS number were collected into a block and matched against each other using a recursive method, that is, matching first with all the remaining records in the block, second with the remaining records, and so on. An exact method of matching was used, namely a link is made only where the NHS number agrees exactly. This was augmented by a set of Boolean logical rules, this permitted the minor variations in date of birth and postcode to be taken into account. Each block was matched eight times using various combinations of the matching variables (Runs 1-8), and then further matched using a random sequence of Runs 1-8. The match rates for the NHS number match are published by Gill (Gill 2004).

The second series of matching runs involved matching all record pairs that had the same date of birth, sex and postcode (DOB/SEX/PCD). The input file contained all the records that had previously been matched on NHS number together with the previous file that did not

contain an NHS number. The file was sorted into: date of birth, record type, sex, postcode and NHS number order. All records having the same DOB/SEX/PCD were collected into the same block. An exact method of matching was used matching records in each block against each other using a recursive method. This was augmented by a set of Boolean logical rules. Each block was matched three times using various combinations of date of birth, sex, postcode and the persons hospital record number (Runs 1-3), and then further matched using a random sequence of Runs 1-3. Records that did not have a valid postcode were excluded from the run, together with those records with dates of birth before 1875 or had the date 19010101. Records with a date of birth 19010101 were processed in a separate run. The match rates for the DOB/SEX/PCD match are published by Gill (Gill 2004).

Following the matching runs, a number of measures were taken to check for errors in the matching process, including printing and manually checking all very large matched blocks to check that they belonged to the same person. Checks were also taken to identify possible twin births to make sure that the records related to two separate babies and efforts were made to identify people with two ONS mortality records.

Following these error checks, records were brought together to provide statistics on the matched pairs including the number of good matches, non-matches, false positives and false negatives. The figures are published by Gill (Gill 2004).

The matched records for a given person were collated together, sorted into person number order, and further sorted on record type and on episode dates within each person number set. The sort order ensured that the last record in every set was the mortality record or the last discharge/transfer. Namely data linkage allows FCEs to be grouped together into one record of a patient's entire inpatient stay, regardless of any inter-hospital transfers which may take place, known as a Continuous Inpatient Spell (CIP). A single CIP may contain information from one of more FCEs. Sorting allows CIP which consists of more than one FCE, to be arranged such that information from the first FCE for that individual’s inpatient

stay, including details of the diagnosis made, is considered the ‘admission record’, and the last record is considered the ‘discharge record’.

A file used for analysis was created, containing all the administrative and clinical data, but excluding any of the matching variables. Variables used for analysis like sex, age and area code were aggregated and stored on the analysis file in such a manner that the record cannot be back-linked and the person identified. A record on the analysis file is referenced to its counterpart on the matching file using the accession number, and the matching file records are encrypted.

Data extraction methods

This section introduces the SAS macro and MS Excel scripts/ spreadsheets used extract the necessary data from the linked dataset and calculate the following statistics;

1. Counts – admissions, discharges, post-admission or post-discharge events
2. Unadjusted rates – post-admission or post-discharge event rates
3. Age and sex truncated rates - post-admission or post-discharge age and sex truncated event rates
4. Age and sex adjusted/ standardised rates - post-discharge age and sex truncated event rates

The first three figures can be enumerated using the SAS macro and the Microsoft (MS) Excel macro written in visual basic (VBA) script. The last figures require the SAS macro and the all MS Excel spreadsheets.

This section will describe the use of the following software analysis tools.

1. SAS macros, called the persoyrs macro (see below for further details)

2. MS Excel macro, written in VBA script called HandleSASOutput

3. MS Excel spreadsheets, called England all-cause mortality 1999-2008 and England specific cause mortality 1999-2008

4. C# script called SASBatcher

The basic concepts and definitions that are used in this section and in the data extraction are below.

A. *Time periods*. There are a number of time periods that must be considered before using this program to define the boundaries of the analysis, including

Inclusion period – this period of time in which patients can included in the study

Follow-up period – is the period of time in which patients are followed for the outcome event of interest

Study period – is equal to the inclusion period and the follow-up period

Period at risk – is the period of time in which the patient is at risk of the outcome event. Ideally it should begin at the same time as the follow-up period to enumerate the total number of events in the period of risk. It should end when the patient is no longer at risk of the outcome event. The characteristics of the period of risk chosen determine the selection of the reference group used in the calculation of SMRs, as it should be theoretically possible for the people within the reference population to be at risk of the outcome event. If you are attempting to compare two populations against a reference population, then the period of risk from which the events are chosen must be fairly compared between the two study populations, this concept was considered in chapter 5 in discussion about suitable comparison groups.

These time periods are operationalised in the SAS program using the following markers (see Appendix 2, Figure 1)

Study start – this is period from which the program starts counting

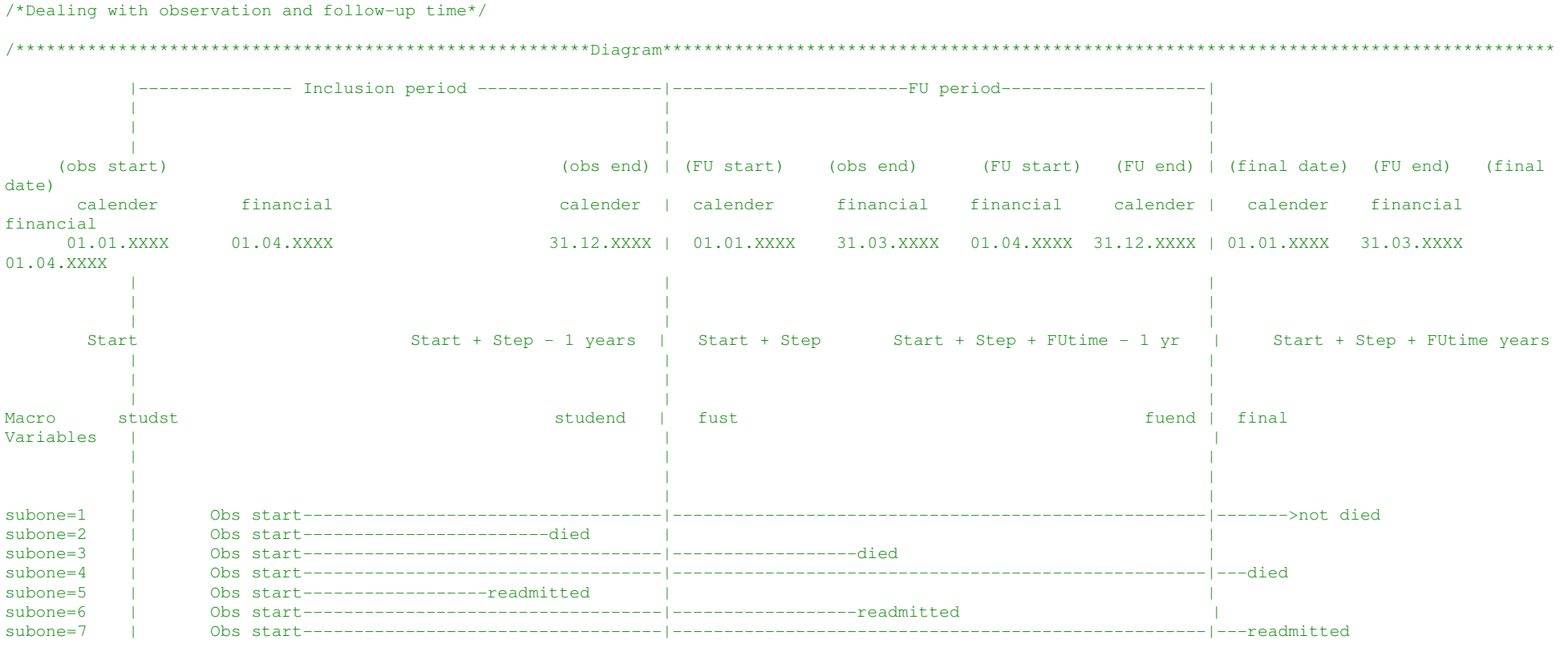
Study end – this is the period from which the program stops counting

Step – this is the inclusion period

FU time – this is the follow-up time

Note that step does not need to equal study end minus study start. Thus you could have multiple inclusion periods between the start and the end of the study. This is equivalent to having multiple consecutive inclusion periods, used for a trend analysis.

Appendix 2, Figure 1 - SAS method for handling study time variables



B. *Inclusion criteria*. The program selects records to count using two types of inclusion criteria

Fixed inclusion criteria are not usually changed by the user with each run. These include criteria such as selecting only England records to include. Other fixed inclusion criteria are – only including those with a date-of-birth (DOB) recorded after the study start, and only those with a gender recorded.

User defined criteria are determined by the user for each study by either changing the SASstring or text inputs files that are needed for each run. These criteria include type of age ranges, time variables, admission source, diagnosis, etc. The diagnosis is selected using Boolean AND/ OR operators.

C. *Outcomes*. All outcomes can be selected by the user by either changing the SASstring or text inputs files that are needed for each run, including the diagnosis with Boolean AND/ OR operators.

D. *Measures*. There are a number of measures that are output or can be calculated using the program

1. Counts - of the number of admissions and discharges by age and sex over a specified time period can be enumerated by running the SAS persoyrs macro
Counts of the number of a specified event following admission or discharge by age and sex over a specified time period can also be enumerated by running the SAS persoyrs macro

2. Proportions and unadjusted rates -

The proportion of events in an admission or discharge population = number of events/ population at risk

Rates of events in an admission or discharge population = number of events/ population at risk in specified time

3. Age and sex standardised rates -

Standardisation is a method of comparing rates from two different populations with different age and sex compositions. It is not a method of controlling for the effects of age/ sex on a disease outcome in one population. Instead it is a method of adjusting rates to give theoretical event rates for populations if they had the same mortality risk as a reference population. Commonly two different methods for standardising event rates are described, namely direct or indirect standardisation (Higham, Flowers et al. 2005);

Direct standardisation – relies on applying an external reference population age/ sex structure to the study population's event rates. This method is commonly used where the study population event rates are stable. It answers the following question – 'what would the number of events be in my study population if it had the same age and sex structure as the reference population'

Indirect standardisation – relies on applying an external reference population event rates to the study's population age/ sex structure. It is useful where the event rates in the study population are not stable/ robust, often due to the small rate of outcomes in the study population. It answers the following question – 'what would the number of events be if my study population had the same mortality risk as the reference population.

Indirect standardisation can give provide a simple measure of relative risk in the study population versus the reference population. This measure is the SMR = observed number of events/ expected number of events in period at risk

Where expected number of events = sum (population in each 5-year age band of study population * event rate for reference population each 5-year age band)

Thus the numbers needed to calculate SMR are as follows (Higham, Flowers et al. 2005)

1. study population in 5-year age bands, by sex
2. observed number of events in 5-year age bands, by sex
3. event rate in the reference population in 5-year age band, by sex

Step-by-step guide to calculating SMRs using the persoyrs SAS macro and MS Excel tools

1. define the time periods you are interested in looking at
2. define and check the fixed inclusion criteria
3. write the text files and SASstring that determine the user defined inclusion criteria
4. write the text files that define the outcomes
5. place the run into the input folder
6. run the C# SASbatcher script
7. pick up the results of the SAS run
8. initiate the HandleSASOutput MS Excel macro on the results of the SAS run
9. merge the results of the SAS run with the MS worksheet containing the relevant reference event rates

Note that steps 1-8 are required to enumerate the study population and observed number of events. Step 9 is used to merge the observed number with the reference event rates to get an expected number of events and an SMR

Appendix 2, Figure 2 - Example of the SASstring used

```
x 'cd O:\Uy\SAS\Output'; /* these two lines of code write the SAS log out to a folder */

proc printto log='O:\Uy\SAS\Output\Disch - AMI - outcome - all deaths.txt';

%personyrs (invariab =, /*where text files containing user defined inclusion criteria are found*/
            infixed =,  /*where text files containing fixed inclusion criteria are found*/
            typecars =, /*selects the type of care recorded included, in association with incg*/
            saslib =,  /*location of a small temporary workspace and where a sample study dataset is output*/
            datafiles =, /*location of the datafiles*/
            incg =, /*also used to select the type of care included*/
            seqnos=, /*selects the record number included*/
            yeartype =, /*selects the type of year, calendar or financial*/
            userstar =, /*defines the start of study, ie. When to start counting*/
            userend =, /*defines the end of study, ie. When to stop counting */
            step =, /*specifies the duration of inclusion for each study in years*/
            FUtime =, /*specifies the duration of FU for event outcomes in years*/
            tcarsrea =, /*used to define the type of outcome searched for*/
            calcpy =, /*whether to calculate person years of follow-up*/
            standard =, /*whether to produced standardised rates - this variable currently does not work*/
            mortali=, /*whether mortality events are searched for*/
            mortality =, /*used defined name for the output*/
            pdatedis =, /*whether to count the number of days from admission or discharge*/
            readm =,/*whether to look for readmissions*/
            runtitle =, /*used defined name for the output, in conjunction with mortality variable*/
            tmpwork =, /*main SAS workspace location*/
            inputfile=, /*name of the SAS data file*/
            strat=, /*1st level of stratification variables - where*/
            strata=, /*1st level of stratification variables - if*/
            stratt=, /*2nd level of stratification variables - where*/
            stratta=, /*2nd level of stratification variables - if*/
            clearlog=, /*whether to clear the internal SAS log*/
            indiviot = /*whether to output a sample study dataset for further analysis*/
            ) ;
```

Appendix 2, Figure 3 - Inputs into the SASstring

```
/* Predictors (start counting obs from      |     macro variable name                    |     Outcome (count final event - mortali)          |   macro variable name
 *             where, subdivided by what)   |                                            |                                                    |
 * ---------------------------------------------------------------------------------------------------------------------------------------------------------------------
 * All admissions to inpt care               pdatedis=jdoa,typecars=1,where incg=1         All readmissions to inpt care                         tcarsrea=1,mortali=readmit
 * Specific admissions to inpt care          pdatedis=jdoa,typecars=1,where incg=0         readmissions to inpt care with specific diag          tcarsrea=1,mortali=shicdrea
 * specific adm for operations               pdatedis=jdoa,typecars=1,where incg=0         readmissions to inpt care for operation               tcarsrea=1,mortali=shicdrea
 *
 * All discharges from daycare services      pdatedis=jdod,typecars=2,where incg=2         All subsequent contact with DC                        tcarsrea=2,mortali=readmit
 * Discharge from DC with specific diag      pdatedis=jdod,typecars=2,where incg=0         subsequent contact with DC with specific diag         tcarsrea=2,mortali=shicdrea
 * Discharge from DC after specific op       pdatedis=jdod,typecars=2,where incg=0         subsequent contact with DC for specific op            tcarsrea=2,mortali=shicdrea
 *
 * All inpatient discharges                  pdatedis=jdod,typecars=1,where incg=1         All subsequent contact with inpt or DC                tcarsrea=3,mortali=readmit
 * Inpt discharges following specific diag   pdatedis=jdod,typecars=1,where incg=0         subsequent contact with inpt/ DC with specific diag   tcarsrea=3,mortali=shicdrea
 * Inpt discharges following operation       pdatedis=jdod,typecars=1,where incg=0         subsequent contact with inpt/ DC for operation        tcarsrea=3,mortali=shicdrea
 *
 * All discharges from DC or inpt care       pdatedis=jdod,typecars=3,where incg=3         All Deaths (from date of death on record)             tcarsrea=4,mortali=mortali
 * discharges from DC or inpt care with Dx   pdatedis=jdod,typecars=3,where incg=0         specific deaths - UC1 (from death cert)               tcarsrea=5,mortali=deasui
 * discharges from DC or inpt for Op         pdatedis=jdod,typecars=3,where incg=0         specific deaths - UC2 (from death cert)               tcarsrea=5,mortali=deasui
 *                                                                                        specific deaths - both (from death cert)              tcarsrea=5,mortali=deasui
 * First Record                              where seqnos = 1                              specific deaths - both (from coroners verdict)       tcarsrea=6,mortali=corsuicbr
 * All Records                               where seqnos = 0
 *
 * Stratify rates by                         strat =  0 = no 1st level stratification
 *                                                    1 = By country (England vs others) - where
 *                                                    2 = By government office region - where
 *                                           strata=  0 = no 1st level stratification
 *                                                    1 = By country (England vs others) - if
 *                                                    2 = By government office region - if
 *
 * Stratify 2nd level rates by               stratt = 0 = no 2nd level stratification
 *                                                    1 = By specialty on admission - where
 *                                                    2 = By specialty on discharge - where
 *                                                    3 = By ethnicity - where
 *                                                    4 = By Marital status - where
 *                                                    5 = By Method of admission - broad categories - where
 *                                           stratta  0 = no 2nd level stratification
 *                                                    1 = By specialty on admission - if
 *                                                    2 = By specialty on discharge - if
 *                                                    3 = By ethnicity - if
 *                                                    4 = By Marital status - if
 *                                                    5 = By Method of admission - broad categories - if
 * Indiviot                                  indiviot 0 = no individual output file for survival analysis
 *                                                    1 = yes individual output file for survival analysis
 * Clearlog                                  clearlog 0 = no clearlog
 *                                                    1 = clears log after end of each loop 1 - allows iteration through user-defined date ranges
 *                                                    2 = clears log after end of each loop 2 - allows iteration through a number of post-discharge FU ranges
 *                                                    3 = clears log after end of each loop 3 - allows iteration through the stratification variable
 *                                                    4 = clears log after setting up the input files and before the datafile is entered
 *                                                    5 = clears log between single and cumulative loops
 * Readmission (for death outcomes)           Readm   0 = don't include readmissions, edate is date of death
 *                                                    1 = do include readmissions, edate is date of admission of subsequent admission
 *
 */
```

Step 1

The following variables in the SASString define the study time parameters

userstar = study start, year when the program starts counting

userend = study end, year when the program stops counting

step = inclusion period in years,

FUtime = determines the totality of the follow up period in years,

The FU time can also be further stratified by the user, by writing non-overlapping time periods in the following text file ‘furange.txt’ and copying this to the location for user defined text files.

You will also have to define the period of risk if you wish to calculate the standardised rates. Note as mentioned earlier in the thesis this program automatically stops counting when the patient is readmitted to hospital or dies i.e. records are censored for these reasons.

Step 2

England only records, records with DOB and gender are all inclusion criteria that are hard-wired into the SAS code. Text files that define the other fixed inclusion criteria that do not vary with each run are in the location defined by the SASstring variable called infixed. The files in this folder include the following;

- fixed inclusion txt files

disposalA.txt – fixed inclusion criteria for disposal method when inca = 1

disposalB.txt - fixed inclusion criteria for disposal method when incb = 1

disposalC.txt - fixed inclusion criteria for disposal method when incc = 1

note that inca, incb and incc are currently set to 0 in the persoyrs macro, however they can be set to 1 depending on which disposal method is chosen.

typecar1.txt – fixed inclusion criteria for type of care

typecar2.txt – fixed inclusion criteria for type of care

typecar3.txt – fixed inclusion criteria for type of care

please note that typecar1, typecar2 and typecar3 are currently not used. Inclusion criteria for type of care is determined by inputs into the SASstring as described below

eleemerg.txt – fixed inclusion criteria for elective vs emergency admissions using HES variable admimeth

- Format files

ADM_TYPE.txt – defines labels for admission type

Admimeth.txt – defines labels for admimeth, elective and emergency admissions

AGEUNITS.txt – defines labels for age units

ASOURCE.txt – defines labels for admission source

BEDSIZE.txt – defines labels for bedsize

Carestate.txt – defines labels for care status

Corverdict.txt - defines labels for coroner's verdict

Country.txt and countr.txt - defines labels for country

DISCSTAT.txt - defines labels for discharge status

dispos1a.txt - defines labels for disposal

ESOP1.txt - defines labels for occupation

ESOP2.txt - defines labels for occupation

Familystate.txt – defines labels for family status

icd9cat.txt – defines labels for ICD9 categories

inclusion.txt – defines labels for inclusion criteria

LAtoSHA.txt – defines labels for LA codes

Legalstatus.txt – defines labels for legal status

LOSFLAG.txt – defines labels for LOS dichotomous variable

Marriages.txt – defines labels for married or not

Marstate.txt – defines labels for marital status

NEWBORN.txt – defines labels for newborns

Ones.txt – used for file management

onesPY.txt – used for file management

Onesstand.txt – used for file management

OWNER.txt – defines labels used for record ownership

previousIPtreat.txt – defines labels used for previous in-patient treatment

RACE.txt - defines labels used for race

REGION.txt - defines labels used for region

Resgor.txt and GOR.txt - defines labels used for government office region

Sex.txt – defines labels used for gender

Sexband.txt – defines labels used for gender

SHA.txt - defines labels used for Strategic Health Authority

Standageband.txt – defines labels used for the standard age bands

Typecare.txt – defines labels used for the type of care

Typeofadm.txt – defines labels used for the type of admission

Step 3 and 4

User-defined inclusion criteria that vary with each run are specified by either inputs into the SASstring or the text files located in the folder defined by the SASstring variable invariab.

They include the following inclusion criteria;

- File locations

a. The location of the log file is determined by inputs into the 1st two lines of the SASstring, as described above
b. The location of user defined text files is determined by the SASstring variable invariab
c. The location of the SAS datafiles is determined by the SASstring variable datafiles
d. The name of the SAS datafile is determined by the SASstring variable inputfile
e. The location of the SAS workspace is determined by the SASstring variables tmpwork (main workspace on a dedicated disk) and saslib (minor workspace on the same disk as the SAS output
f. The location of SAS output is also determined by the SASstring variable invariab (note that the output and the user defined text files and SASstring are all contained to the same folder)

- Age band

The analysis is stratified by sex automatically. Age stratification is determined by the user, by selecting non-overlapping age bands. There are 19 default age bands as per UHCE protocols. However any age bands can be defined by writing 'ageband.txt' and copying this to the location for user defined text files.

- Selection of records to include – admission/ discharge records, type of care, record sequence number and diagnosis

The type of record selected, i.e. whether an admission/ discharge record is selected, what type of care is included and the record number included is all determined by inputs into the SASstring

The specific diagnosis of records to include is determined by the following text file inputs located in the folder defined by the SASstring variable invariab;

Diagnosis on admission – Main (i.e. position 8), ICD10 codes - ICDdiagdis10mainadm.txt

Any (i.e. positions 8 to 14), ICD10 codes - ICDdiagdis10anyadm.txt

Main (i.e. position 8), ICD9 codes - ICDdiagdis9mainadm.txt

Any (i.e. positions 8 to 14), ICD9 codes – ICDdiagdis9anyadm.txt

Main (i.e. position 8), ICD8 codes – ICDdiagdis8mainadm.txt

Any (i.e. positions 8 to 14), ICD8 codes – ICDdiagdis8anyadm.txt

Diagnosis on discharge – Main (i.e. position 1), ICD10 codes - ICDdiagdis10maindis.txt

Any (i.e. positions 1 to 7), ICD10 codes - ICDdiagdis10anydis.txt

Main (i.e. position 1), ICD9 codes – ICDdiagdis9maindis.txt

Any (i.e. positions 1 to 7), ICD9 codes – ICDdiagdis9anydis.txt

Main (i.e. position 1), ICD8 codes – ICDdiagdis8maindis.txt

Any (i.e. positions 1 to 7), ICD8 codes – ICDdiagdis8anydis.txt

Diagnosis anywhere on the record –i.e. positions 1 to 14, ICD10 codes - ICDdiagdis10any.txt

i.e. positions 1 to 14, ICD9 codes – ICDdiagdis9any.txt

i.e. positions 1 to 14, ICD8 codes – ICDdiagdis8any.txt

Operative codes – positions 1 to 12, OPCS 4 codes - OPCSdiagdis4.txt

positions 1 to 12, OPCS 3 codes – OPCSdiagdis3.txt

positions 1 to 12, OPCS 2 codes – OPCSdiagdis2.txt

positions 1 to 12, OPCS 1 codes – OPCSdiagdis1.txt

Note that the text files are structured in such a way as to allow Boolean AND/ OR selection of diagnosis within one ICD version, as well as combinations of diagnostic and operative codes across different ICD/ OPCS versions

The selection of codes is performed by the following SAS macros in the persoyrs collection

- discharg
- dischar1
- dischar2

    - dischargsum
    - dischargsumm

An accompanying MS word file named 'DISCHARG_table.doc' in the SAS macro folder contains a list of the specific sequence of diagnosis selected to facilitate debugging these files.

- Selection of the type of outcome recorded – all-cause mortality, all readmissions and specific event outcomes

Outcomes that are selected can also determined by user input into the SASstring and the user defined text files, especially the SASstring variables tcarsea and mortali (see above). If all readmissions or all deaths are selected in the SASstring then the text files will not be used to select specific diagnosis. If a specific diagnosis outcome is selected the record chosen is determined by the following text file inputs in the folder defined by the SASstring variable invariab;

Admission diagnosis on readmission –

Main (i.e. position 8), ICD10 codes - ICDdiagrea10mainadm.txt

Any (i.e. positions 8 to 14), ICD10 codes - ICDdiagrea10anyadm.txt

Main (i.e. position 8), ICD9 codes - ICDdiagres9mainadm.txt

Any (i.e. positions 8 to 14), ICD9 codes – ICDdiagres9anyadm.txt

Main (i.e. position 8), ICD8 codes – ICDdiagres8mainadm.txt

Any (i.e. positions 8 to 14), ICD8 codes – ICDdiagres8anyadm.txt

Discharge diagnosis on readmission –

Main (i.e. position 1), ICD10 codes - ICDdiagrea10maindis.txt

Any (i.e. positions 1 to 7), ICD10 codes - ICDdiagrea10anydis.txt

Main (i.e. position 1), ICD9 codes – ICDdiagrea9maindis.txt

Any (i.e. positions 1 to 7), ICD9 codes – ICDdiagrea9anydis.txt

Main (i.e. position 1), ICD8 codes – ICDdiagrea8maindis.txt

Any (i.e. positions 1 to 7), ICD8 codes – ICDdiagrea8anydis.txt

Diagnosis anywhere on the record on readmission–

i.e. positions 1 to 14, ICD10 codes - ICDdiagrea10any.txt

i.e. positions 1 to 14, ICD9 codes – ICDdiagrea9any.txt

i.e. positions 1 to 14, ICD8 codes – ICDdiagrea8any.txt

Operative codes on readmission –

positions 1 to 12, OPCS 4 codes - OPCSdiagrea4.txt

positions 1 to 12, OPCS 3 codes – OPCSdiagrea3.txt

positions 1 to 12, OPCS 2 codes – OPCSdiagrea2.txt

positions 1 to 12, OPCS 1 codes – OPCSdiagrea1.txt

Specific causes of death –

Underlying cause 1 (i.e. position 1), ICD10 - ICDoutcome10uc1.txt

Underlying cause 2 (i.e. position 11), ICD10 - ICDoutcome10uc2.txt

Underlying cause 1 or 2 (i.e. positions 1 to 16), ICD10 - ICDoutcome10all.txt

Underlying cause 1 (i.e. position 1), ICD9 – ICDoutcome9uc1.txt

Underlying cause 2 (i.e. position 11), ICD9 – ICDoutcome9uc2.txt

Underlying cause 1 or 2 (i.e. positions 1 to 16), ICD9 – ICDoutcome9all.txt

Underlying cause 1 (i.e. position 1), ICD8 – ICDoutcome8uc1.txt

Underlying cause 2 (i.e. position 11), ICD8 – ICDoutcome8uc2.txt

Underlying cause 1 or 2 (i.e. positions 1 to 16), ICD8 – ICDoutcome8all.txt

Note again that the text files are structured in such a way as to allow Boolean AND/ OR selection of diagnosis within one ICD version, as well as combinations of diagnostic and operative codes across different ICD/ OPCS versions

The selection of codes is performed by the following SAS macros in the persoyrs collection

outcome

outcome1

outcome2

outcome5

outcomesum

outcomesumm

outcomesums

The MS word file named 'DISCHARG_table.doc' in the SAS macro folder also contains a list of the specific sequence of diagnosis selected by these macros to facilitate debugging these files.

- Selection of the specific type of analysis – year type, stratification by geographical area

The analysis can be performed by calendar year or financial year depending on whether cadatecal or fndatecal is specified in the SASstring respectively. The analysis can be stratified by geographical region depending on the inputs to the SASstring variable strat (see

above). Person years of follow-up can be calculated by specifying the SASstring variable calcpy (currently not working).

- Naming the run

The folder names are determined by the user. The filenames in the output folder is determined automatically. The heading within each file is determined by the SASstring variable runtitle. The sub-heading is determined by the SASstring variable mortality.

- other user defined criteria

Lastly the SASstring variable clearlog allows users to specify when the internal SAS log is cleared (see above). This will not affect the log file written to an external txt file. Users can specify a sample dataset output into the folder location specified in the SASstring variable saslib to double check the analysis and to conduct survival analysis, by setting the SASstring variable indiviot to 1.

Step 5

Once the SASstring and text files are finalised, then copy the contents into the input folder.

Step 6 and 7

Run the C# script named SASBatcher. It will automatically pick the contents of the input file, move the contents to the default output folder, run SAS, and activate the SAS macro named persoyrs. Once the analysis has finished it will automatically move the files from the output folder and the saslib folders back to the input folder

Step 8

Once the analysis is complete the following files should be in the moved from the output folder to the input folder automatically by the C# script named SASBatcher.

- List of files divided by year of included records, and follow-up periods for events of interest.

The files should also be divided into singular and cumulative analysis. Singular analysis records the number of events between the start of each FU stratification period and the date of the outcome or the end of the next FU stratification period, ie counts from the start of the FU stratification period rather than the start of the study. Cumulative analysis looks at the cumulative number of events from the date that records were included until the outcome, or the end of the FU stratification period, i.e counts from the start of the study.

Run the HandleSASoutput MS Excel VBA script. This will bring all the files containing singular analysis together, and all the files containing cumulative analysis together. Into the following files

Singular analysis –

indSummary_sing – gives the demographic profile of the cohort being examined at the start of each FU stratification period
totSummary_sing – gives the count of the number of records and people in the cohort, and the number of events at the FU stratification period

Cumulative analysis –

indSummary_cum – gives the demographic profile of the cohort being examined since the start of the study

totSummary_cum – gives the count of number of records and people in the cohort, and the number of events since the start of the study and the end of the FU stratification period in question

Counts and unadjusted event rates can be calculated from spreadsheet totsummary_cum, as explained above. In order to calculate adjusted rates then proceed to step 9.

The spreadsheet totsummary_cum contains the following worksheets

Worksheet 1 – contains a cumulative count of all the records (spells if the CIPS file is being used, FCEs if the FCE file is being used) by sex, age band and FU stratification period
Worksheet 6 – contains a cumulative count of the number of people by sex, age band and FU stratification period
Worksheet 2 – contains a cumulative count of the observed number of events by sex, age band and FU stratification period

Step 9

In this booklet I shall focus on the calculation of age/ sex standardised mortality rates. Note that we are standardising to the English national population using the 'indirect method' to enable the calculation of a standardised mortality ratio, SMR.

Open the excel spreadsheets totsummary_cum, and England all-cause mortality 1999-2008 or England specific cause mortality 1999-2008 depending on whether you are calculating standardised all-cause mortality rates or specific cause mortality rates.

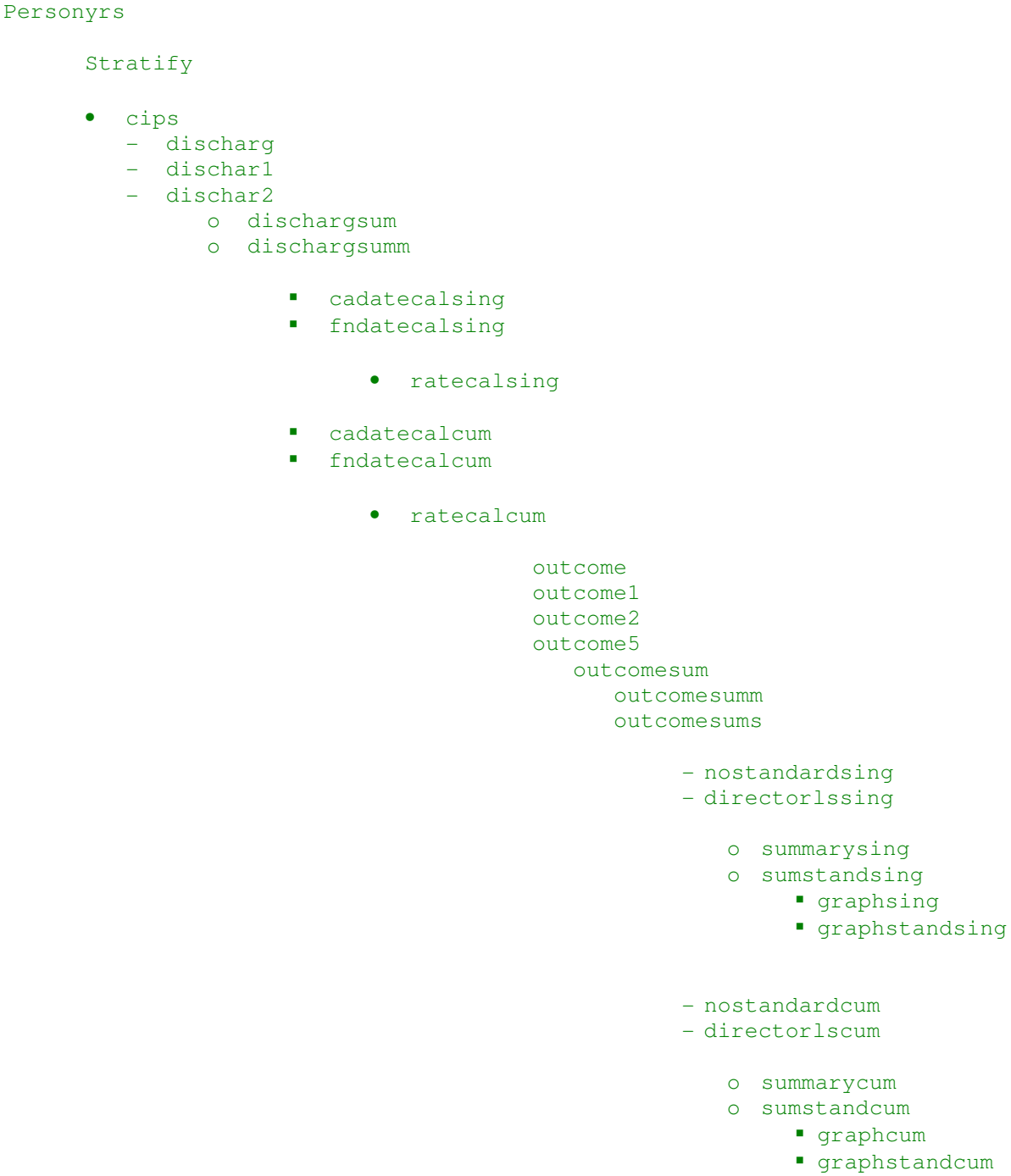
Copy the contents of the worksheet named 'Mortality Rates' from the spreadsheet England all-cause mortality 1999-2008 or England specific cause mortality 1999-2008 into the

spreadsheet totsummary_cum. ‘Mortality Rates’ contains the national/ reference mortality rates rate by sex, and age band.

Apply these national mortality rates to the number of people in the study cohort in each sex and each age band. This will give you the expected number of events in each sex and age band. Sum the expected number of events in each sex and age band to get a total number of expected events.

The SMR is the total observed number of events/ total expected number of events.

Appendix 2, Figure 4 - Sequence of SAS macros in the persoyrs collection



Function of the macros in the persoyrs collection

SAS macro – personyrs, stratify and cips

1. extract of ORLS (1979-1999) and HES (2000-2005) data with suitable variables

2. appending ORLS and HES to create a combined dataset covering all hospital discharges between 1979 and 2005

3. Applying exclusion criteria to the combined dataset (inc missing DOB, sex, and type of discharge/ disposal)

4. Identifying a suitable cohort of records (i.e. flagging predictor variables)

5. Stratifying the dataset by the where or if statement

SAS macros - cadatecal (calendar year) & fndatecal* (financial year)*

6. splitting the combined dataset into suitable time periods to facilitate examination of time trends. This will involve decisions regarding suitable periods to observe cohorts of patients who were discharged from hospital and suitable periods following the end of sampling to continue to observe the cohort for outcomes

SAS macro – ratecal (cumulative and singular)*

7. identifying relevant age groups in which to tally outcomes and calculate rates

8. identifying relevant FU periods in which to tally outcomes and calculate rates

Note that these boundaries enable the calculation of person years of follow-up

SAS macro – Direct & nostandard* - Sum* - graph**

9. Counting the number of events in specified age groups and over the specified FU periods following hospital discharge

10. Counting the number of individuals to calculate the event rate per 1,000 individuals over the period of time

11. Tallying the total FU time to enable the calculation of event rates per person years of FU

12. Outputting the data to CSV files and SAS graphs of trends

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08 February 2005

Professor Michael Goldacre
Professor of Public Health, Oxford University
Oxford University
Unit of Health-Care Epidemiology, Department of Public Health,
Old Road Campus, Old Road,
Oxford OX3 7LF

Dear Professor Goldacre

Full title of study: *Epidemiological and health services research using routine NHS data: work programme of the Unit of Health-Care Epidemiology, Oxford University, funded by the National Co-ordinating Centre for Research Capacity Development*
REC reference number: *04/Q2006/176*
Protocol number:

Thank you for your letter of 31 January 2005, responding to the Committee's request for further information on the above research.

The further information was considered at the meeting of the Sub-Committee of the REC held on 04 February 2005. A list of the members who were present at the meeting is attached.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation.

The sub-committee felt it would be a good idea if we could have periodic reports, say every two years, on the progress of this study, with a summary of the direction in which the research will then proceed.

The Committee has designated this study as having "no local investigators". There is no requirement for [other] Local Research Ethics Committees to be informed or for site-specific assessment to be carried out at each site.

Conditions of approval
The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents
The final list of documents reviewed and approved by the Committee is as follows:

Document Type:	Version:	Dated:	Date Received:
Application	1	29/10/2004	01/11/2004
Investigator CV		29/10/2004	01/11/2004
Protocol	corecuhce1	29/10/2004	02/11/2004
Covering Letter		29/10/2004	01/11/2004
Response to Request for Further Information letter		31/01/2005	03/02/2005
letter from DoH		30/12/2004	03/02/2005
Further information & clarification			03/02/2005
Authorisation of access to data files		29/10/2004	01/11/2004

Management approval
You should arrange for all relevant NHS care organisations to be notified that the research will be taking place, and provide a copy of the REC application, the protocol and this letter.

All researchers and research collaborators who will be participating in the research must obtain management approval from the relevant care organisation before commencing any research procedures. Where a substantive contract is not held with the care organisation, it may be necessary for an honorary contract to be issued before approval for the research can be given.

Membership of the Committee
The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Notification of other bodies
The Committee Administrator will notify the research sponsor that the study has a favourable ethical opinion.

Statement of compliance
The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

04/Q2006/176	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project,

Yours sincerely,

Dr David Grier
Chair

Enclosures *List of names and professions of members who were present at the meeting and those who submitted written comments*

Standard approval conditions

Enclosure 1

List of names and professions of members who were present at the meeting and those who submitted written comments

Dr David Grier
Consultant Paediatric Radiologist

Mr Stephen Brown
Director of Pharmacy

Unit of Health-Care Epidemiology
Department of Public Health

Old Road Campus, Roosevelt Drive, Headington, Oxford OX3 7LF, UK
Tel: +44 (0)1865 289377, Fax: +44 (0)1865 289379, E-mail: Michael.goldacre@dphpc.ox.ac.uk

April 27th 2012

The Chairman
Health Research Authority
National Research Ethics Service (NRES)
Bristol REC Centre
Level 3 Block B
Whitefriars
Lewins Mead
Bristol, BS1 2NT

Dear Chairman

REC reference number: 04/Q2006/176

Epidemiological and health services research using routine NHS data: work programme of the Unit of Health-Care Epidemiology, Oxford University, funded by the National Institute for Health Research (RNC/035/002). ***Note: was previously funded by the National Co-ordinating Centre for Research Capacity, it is the same work but the name of the funding body has changed.***

Our original submission was for a programme of work funded to March 2012. We now have funding to July 2013. We should be grateful for advice on what, if anything in addition to the enclosures, we should do to apply for an extension to March 2015.

pp Michael Goldacre.

Yours sincerely

Professor Michael Goldacre
Professor of Public Health
University of Oxford

NHS
Health Research Authority

ANNUAL PROGRESS REPORT TO MAIN RESEARCH ETHICS COMMITTEE
(For all studies except clinical trials of investigational medicinal products)

To be completed in typescript and submitted to the main REC by the Chief Investigator. For questions with Yes/No options please indicate answer in bold type.

1. Details of Chief Investigator

Name:	**Professor Michael Goldacre**
Address:	**University of Oxford** **Unit of Health-Care Epidemiology** **Department of Public Health, Old Road campus** **Roosevelt Drive, Headington** **Oxford , OX3 7LF**
Telephone:	**01865 289377**
E-mail:	**Michael.goldacre@dph.ox.ac.uk**
Fax:	**01865 289379**

2. Details of study

Full title of study:	**Epidemiological and health services research using routine NHS data: work programme of the Unit of Health-Care Epidemiology, Oxford University, funded by the National Institute for Health Research (RNC/035/002)**
Name of main REC:	**North Somerset & South Bristol Research Ethics Committee**
REC reference number:	**04/Q2006/176**
Date of favourable ethical opinion:	**09 January 2007**
Sponsor:	**Department of Health**

3. Commencement and termination dates

Has the study started?	***Yes***
If yes, what was the actual start date?	**09 January 2007**
If no, what are the reasons for the study not commencing? What is the expected start date?	
Has the study finished?	***No***

If yes, complete and submit "Declaration of end of study" form, available at http://www.nres.npsa.nhs.uk/applications/after-ethical-review/endofstudy/	

If no, what is the expected completion date? *If you expect the study to overrun the planned completion date this should be notified to the main REC for information.*	**The study is now funded until July 31st 2013**
If you do not expect the study to be completed, give reason(s)	**Application for further funding to extend the study will be submitted before the end date**

4. Site information

Do you plan to increase the total number of sites proposed for the study? If yes, how many sites do you plan to recruit?	***No***

5. Recruitment of participants

In this section, "participants" includes those who will not be approached but whose samples/data will be studied.

Number of participants recruited:	*Proposed in original application:* *Actual number recruited to date:* ***Not applicable*** ***(it is an anonymised dataset)***
Number of participants completing trial:	*Actual number completed to date:* ***Not applicable***
Number of withdrawals from study to date due to: (a) withdrawal of consent (b) loss to follow-up (c) death (where not the primary outcome) Total study withdrawals:	***Not applicable***
*Number of treatment failures to date (prior to reaching primary outcome) due to: (a) adverse events (b) lack of efficacy Total treatment failures: ** Applies to studies involving clinical treatment only*	***Not applicable***
Have there been any serious difficulties in recruiting participants?	***Not applicable***
If Yes, give details:	
Do you plan to increase the planned recruitment of participants into the study? *Any increase in planned recruitment should be notified to the main REC as a substantial amendment for ethical review.*	***Not applicable***

6. Safety of participants

Have there been any related and unexpected serious adverse events (SAEs) in this study?	***No***
Have these SAEs been notified to the Committee? *If no, please submit details with this report and give reasons for late notification.*	***Not applicable***
Have any concerns arisen about the safety of participants in this study? *If yes, give details and say how the concerns have been addressed.*	***Not applicable***

7. Amendments

Have any substantial amendments been made to the trial during the year?	***No***
If yes, please give the date and amendment number for each substantial amendment made.	

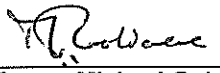
8. Serious breaches of the protocol

Have any serious breaches of the protocol occurred during the year? *If Yes, please enclose a report of any serious breaches not already notified to the REC.*	***No***

9. Other issues

Are there any other developments in the study that you wish to report to the Committee?	***No***
Are there any ethical issues on which further advice is required? *If yes to either, please attach separate statement with details.*	***No***

10. Declaration

Signature of Chief Investigator:	
Print name:	**Professor Michael Goldacre** **Professor of Public Health**
Date of submission:	**April 24th 2012**

NRES Committee South West - Central Bristol
Whitefriars
Level 3, Block B
Lewin's Mead
Bristol BS1 2NT
Email: ubh-tr.SouthWest3@nhs.net

Tel: 0117 342 1335
Fax: 0117 342 0445

07 June 2012

Professor Michael Goldacre
Professor of Public Health, Oxford University
Oxford University
Unit of Health-Care Epidemiology, Department of Public Health,
Old Road Campus, Old Road,
Oxford OX3 7LF

Dear Professor Goldacre

Study title:	**Epidemiological and health services research using routine NHS data: work programme of the Unit of Health-Care Epidemiology, Oxford University, funded by the National Co-ordinating Centre for Research Capacity Development**
REC reference:	**04/Q2006/176**

Thank you for sending the progress report for the above study dated 24 April 2012. The report will be reviewed by the Chair of the Research Ethics Committee, and I will let you know if any further information is requested.

The favourable ethical opinion for the study continues to apply for the duration of the research as described in the **progress report,** application and protocol agreed by the REC, taking account of any substantial amendments.

04/Q2006/176:	**Please quote this number on all correspondence**

Yours sincerely

Mrs Naazneen Nathoo
Committee Co-ordinator

Appendix 5 - Proposed causes of avoidable (amenable and preventable) mortality: ICD–10 codes and age limits

Condition group and cause	ICD10 codes	Age groups	Amenable to medical treatment	Preventable with public health intervention
Infections				
Intestinal infectious diseases	A00–A09	0–14	●	
Tuberculosis	A15–A19, B90	0–74	●	●
Other infections (diphtheria, other tetanus, acute poliomyelitis)	A35– A36, A80	0–74	●	●
Whooping cough	A37	0–14	●	●
Selected invasive bacterial and protozoal infections	A38–A41, A46, A48.1, B50–B54, G00, G03, L03	0–74	●	
Measles	B05	1–14	●	●
Viral hepatitis	B15–B19	0–74		●
HIV/AIDS	B20–B24	All		●
Neoplasms				
Malignant neoplasm of lip, oral cavity and pharynx	C00–C14	0–74		●
Malignant neoplasm of oesophagus	C15	0–74		●
Malignant neoplasm of stomach	C16	0–74		●
Malignant neoplasm of colon and rectum	C18–C21	0–74	●	
Malignant neoplasm of liver	C22	0–74		●
Malignant neoplasm of trachea, bronchus and lung	C33–C34	0–74		●
Malignant melanoma of skin	C43	0–74	●	●
Other malignant neoplasms of skin	C44	0–74	●	●
Malignant neoplasms of breast	C50	0–74	●	
Malignant neoplasm of cervix uteri	C53	0–74	●	
Malignant neoplasm of corpus uteri and uterus unspecified	C54–C55	0–44	●	
Malignant neoplasm of testis	C62	0–74	●	
Malignant neoplasm of bladder	C67	0–74	●	
Malignant neoplasm of thyroid gland	C73	0–74	●	
Hodgkin's disease	C81	0–74	●	
Leukaemia	C91–C95	0–44	●	
Benign neoplasms	D10–D36	0–74	●	

Nutritional, endocrine and metabolic				
Disorders of thyroid gland	E00–E07	0–74	●	
Diabetes mellitus	E10–E14	0–49	●	
Drug use disorders				
Alcohol related diseases, excluding external causes	F10, G31.2, G62.1, I42.6, K29.2, K70, K73, K74 (excl. K74.3–K74.5), K86.0	0–74		●
Illicit drug use disorders	F11–F16, F18–F19	0–74		●
Neurological disorders				
Epilepsy and status epilepticus	G40–G41	0–74	●	
Cardiovascular diseases				
Rheumatic and other valvular heart disease	I01–I09	0–74	●	
Hypertensive diseases	I10–I15	0–74	●	
Ischaemic heart disease	I20–I25	0–74	●	●
DVT with pulmonary embolism	I26, I80.1–I80.3, I80.9, I82.9	0–74		●
Cerebrovascular diseases	I60–I69	0–74	●	
Aortic aneurysm and dissection	I71	0–74		●
Respiratory diseases				
Other respiratory	J00–J08, J20–J39, J47 – J99	1–14	●	
Influenza (including swine flu)	J09–J11	0–74	●	●
Pneumonia	J12–J18	0–74	●	●
Chronic Obstructive Pulmonary Disorder	J40–J44	0–74	●	●
Asthma	J45– J46	0–74	●	
Digestive disorders				
Gastric and duodenal ulcer	K25–K28	0–74	●	
Acute abdomen, appendicitis, intestinal obstruction, cholecystitis / lithiasis, pancreatitis, hernia	K35–K38, K40–K46, K80–K83, K85–K86, K91.5	0–74	●	

Genitourinary disorders				
Nephritis and nephrosis	N00–N07, N17–N19, N25, N27	0–74	•	
Obstructive uropathy & prostatic hyperplasia	N13, N20–N21, N35, N40, N99.1	0–74	•	
Maternal & infant				
Pregnancy, childbirth and the puerperium	O00 – O99	All	•	
Complications of perinatal period	P00–P96, A33	All	•	
Congenital malformations, deformations and chromosomal anomalies	Q00–Q99	0–74	•	
Unintentional injuries				
Transport Accidents	V01–V99	All		•
Accidental Injury	W00–X59	All		•
Intentional injuries				
Suicide and self inflicted injuries *	X60–X84, Y10–Y34	All		•
Homicide/ Assault	X85–Y09, U50.9	All		•
Misadventures to patients during surgical and medical care	Y60–Y69, Y83–Y84	All	•	

* Note that deaths from suicide and intentional injuries (ICD10 codes - X60–X84, Y10–Y34) was counted within our calculations where this cause was recorded anywhere on the death certificate, as opposed to the underlying cause only.